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1955

MYOGLOBINURIA IN MAN

With Special Reference to a Familial Form

BY

RAGNAR HED

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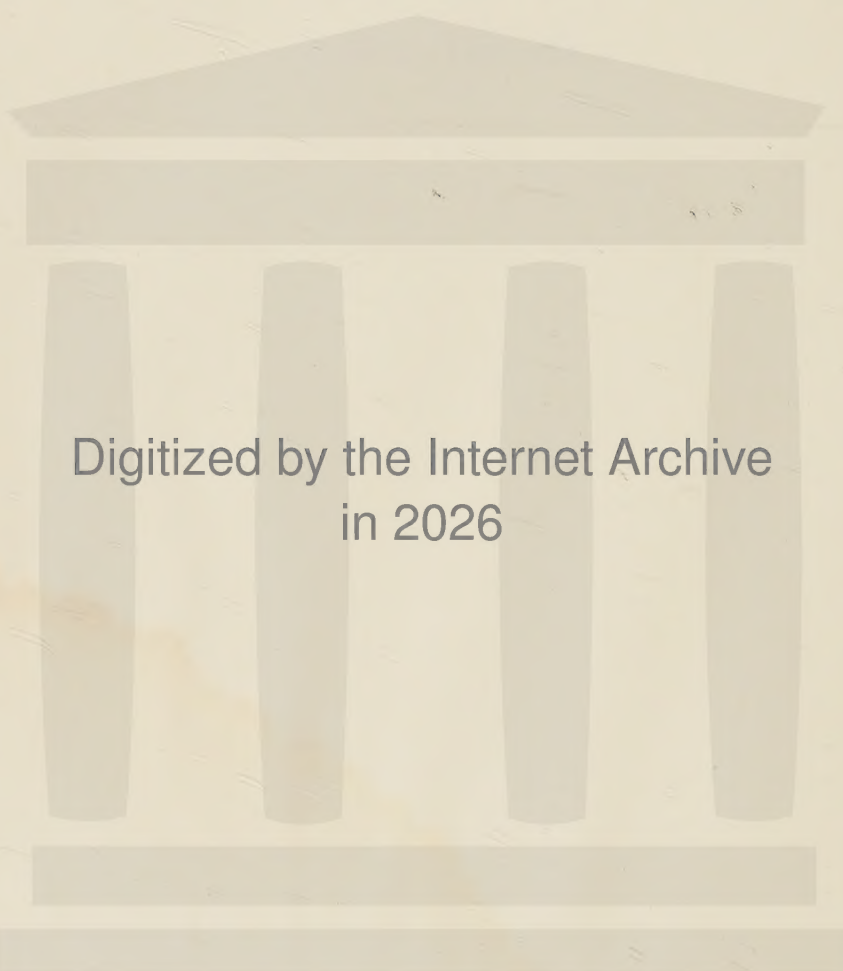
STOCKHOLM 1955

Translated from the Swedish

by

ERICA ODELBERG

TO MY WIFE
AND CHILDREN



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PREFACE

The present study was carried out at Medical Department IV of Södersjukhuset, Stockholm. I wish to express my sincere gratitude to my Chief, Docent Sixten Kallner, for his unfailing interest and constant encouragement in the course of the investigation.

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Stockholm, April 1955.

Ragnar Hed

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INTRODUCTION

About 10 years ago, I had the opportunity of observing my first case of paroxysmal myoglobinuria when serving at a military hospital in northern Sweden. A closer study of this case revealed three facts which decided me to learn as much as possible about myoglobinuria in man.

Firstly, the patient informed me that he had two brothers probably suffering from the same syndrome. This could easily be confirmed by a subsequent clinical investigation of these two cases. The occurrence of myoglobinuria in three brothers raised the question of whether or not genetic factors play any role in its aetiology. Secondly, the history of all three patients showed that the attacks were precipitated by hard exercise and by insufficient intake of food. This aroused the suspicion that there might be an inborn metabolic disturbance. Finally, my first approach to the literature on myoglobinuria in man and in domestic animals showed that the disease is associated with several problems of interest in general medicine and in biochemistry.

My interest in myoglobinuria has continued during my service at various hospitals in different parts of Sweden. During this time, I have been able to study an additional three cases of myoglobinuria, one investigated personally, and the other two on the basis of information kindly placed at my disposal by colleagues. My series thus consists of six cases of myoglobinuria, representing several different types of the disease. Brief reports of these cases have already been published in various journals (Hed 1947, 1951, 1953, Hed, Iggbom & Wahlgren 1955, Hed, Larsson & Wahlgren 1955).

The object of the present paper is to give a more detailed account of the clinical study of these cases, and to discuss the relationship of the results to the observations on myoglobin and myoglobinuria in man and in domestic animals made by other writers. It must, however, be stressed that the study is a clinical one. Although several interesting biochemical problems are touched on, no attempt has been made at a closer analysis of them, since such matters lie beyond the scope of my qualifications.

The paper is divided into two parts. In Chapter I of Part One, a brief survey is given of the chemical and physiological properties of myoglobin. Chapter II comprises a short account of myoglobinuria in domestic animals. Chapter III deals with problems concerning the classification of different types of myoglobinuria in man. The cases of myoglobinuria reported in the literature are also briefly reviewed and discussed in this chapter.

Part Two comprises an account and discussion of my six cases of myoglobinuria. The case material and the methods of investigation are presented in Chapter IV. Chapters V and VI deal with the familial type of paroxysmal myoglobinuria from the clinical and genetic aspects, respectively. The remaining three cases are described and discussed in Chapter VII. This is followed by a general summary.

PART ONE

Myoglobin. — Myoglobinuria in Domestic
Animals and in Man

MYOGLOBIN

1. *Historical Survey*

The red colour of mammalian muscles was originally attributed to the presence of blood, and was therefore regarded as depending on the blood pigment. As early as 1850, Kölliker put forward the hypothesis that the muscles contained a special red pigment to which their colour was due. In 1865, Kühne demonstrated that the muscles retained their red colour even after the blood had been removed by washing. He did not, however, abandon the view that the muscle pigment was identical with the blood pigment, although he ascribed a special function to the former. Lankester, in 1871, observed that the pharynx muscles of a species of mollusc were red and, as he presumed, contained blood pigment, despite the fact that the blood of the animal in question was colourless. Consequently, what was believed to be blood pigment was present in the muscles only, whereas it was entirely lacking in the blood. For this reason, the pigment was presumed to differ in origin from the blood and the haematopoietic organs.

Mörner was the first to establish definitely that the muscle pigment is a special substance, differing distinctly from the blood pigment. His observations, published in 1897, were made in experiments on the dog, horse and cattle, performed as follows. The animals were exsanguinated, the arteries flushed through and the muscles washed with physiological saline solution, after which an extract was prepared from the muscles. This muscle extract was compared spectroscopically with haemolyzed blood, diluted to the same colour intensity. The absorption bands of the muscle pigment were then found to lie somewhat closer to the red range of the spectrum than did those of haemoglobin. The respective figures were 581.5 $m\mu$ and 543.5 $m\mu$ for the muscle pigment, and 577.5 $m\mu$ and 540 $m\mu$ for the haemoglobin. Although this difference was small, it was conclusive, and it appeared even when the solutions were reduced, or treated with potassium ferricyanide or with carbon monoxide.

Mörner also studied the haemin of the two pigments. Haemin crystals from the muscle pigment had already been isolated by Kühne in 1865, but they had not been submitted to spectroscopic analyses. Mörner found that haemin crystals from muscle pigment and from blood pigment had identical absorption spectra. He therefore concluded: "Bis auf weiteres muss man daher eine Verschiedenheit des Eiweisscomponenten oder der Bindung zwischen diesem und dem farbigen Componenten an nehmen." These observations led Mörner to infer that the muscle pigment and the blood pigment, which had earlier been regarded as identical, were two different substances and,

consequently, that the former should be given a special name. He wrote: "Ein Name wie 'Myoglobin' dem Hämoglobin nachgebildet, wäre nicht zweckentsprechend. Da der hämoglobinähnliche Muskelfarbstoff, wenn auch nicht der einzige, so doch der bedeutungsvollste Muskelfarbstoff ist, will ich für ihn den Namen *Myochrom* vorschlagen." It was not, however, until 1921 that the term myoglobin was introduced by Günther, and was thereafter generally accepted. Mörner's work did not arouse the attention it deserved. Thirty years elapsed before his discovery became common knowledge, and it was as late as 1932 when efforts to isolate the substance in the crystalline form were first successful.

During the first decades of the present century, the question of the nature of the muscle pigment was mainly of interest in veterinary medicine. The horse was found to be subject to a disease known as lumbar paralysis or "Kreuzlähme" (see p. 18), characterized by painful hardening of the muscles and passage of red-coloured urine. The colour of the urine was considered to be due to the presence of haemoglobin. As early as 1884, Fröhner expressed the view that this pigment was derived from the muscles. His statement was based on the finding that the muscles at the affected sites were grey or less strongly coloured than the rest of the muscles. But it was not until 1930 that Carlström, applying Mörner's spectral analysis, was able to establish that myoglobin was excreted in the urine in this disease in the horse.

In the early years of this century, Camus & Pagniez (1902) made a number of investigations to determine the physiological properties of the muscle pigment. They had observed that although, in the disease in question in the horse, the urine was dark, owing — as it was assumed — to the presence of haemoglobin, the serum was colourless. This was inexplicable if the colour was a result of haemolysis in the blood stream. The authors compared the conditions in paroxysmal haemoglobinuria in man, and found that the serum was red in the latter. They then approached the problem of whether the dark pigment in the urine could derive from the muscles. In experiments on the dog and the rabbit, they found it possible to induce haemoglobinuria by the injection of haemolyzed blood into the blood stream. It was, however, necessary to inject relatively large amounts before the serum assumed a red colour. If they instead injected only a small quantity of muscle juice, the urine became discoloured and the serum remained colourless. This permitted the inference that the muscle pigment more easily passed through the kidneys than did the blood pigment. Camus & Pagniez verified their experiments in several species of animals, and their observations were confirmed in 1910 by Meyer-Betz.

2. Chemical and Physiological Properties

In 1932, Theorell succeeded in isolating myoglobin in the crystalline form from the heart of the horse, and in 1947 Theorell & de Duve obtained crystalline myoglobin from the urine of a human subject with myoglobinuria (Case 2, p. 46). These

achievements made it possible to carry out detailed studies of the chemistry of myoglobin.

In a series of publications in 1934, Theorell gave accounts of the absorption spectra of oxy-, carboxy-, met- and reduced myoglobin, and of their oxygen dissociation curves. The following data regarding myoglobin are now generally accepted.

With respect to its *chemical structure*, myoglobin — like haemoglobin — belongs to the haemoproteins, and consists of a protoporphyrin component and a globin component. The protoporphyrin is the same in myoglobin and in haemoglobin, consisting of four pyrrole rings, in the centre of which one iron atom is attached to four nitrogen atoms. Thus, in this respect, myoglobin and haemoglobin differ only with regard to the globin fractions, as Möerner already pointed out in 1897. Both contain 0.345 per cent of iron. Maeda (1939) demonstrated, by means of immune biological studies, that the globin components of myoglobin and of haemoglobin differ in type. Rossi-Fanelli's investigation of 1948 also argues in favour of this view. He determined the amino acid composition of the respective globin components, and found that myoglobin had a considerably higher lysine content than haemoglobin but an appreciably lower arginine content. Several authors have suggested that two forms of myoglobin may exist, one foetal and one adult, in similarity to haemoglobin. The investigations of Jonxis & Wadman (1952) indicate that this is probably so. The authors were not, however, able to demonstrate any such differences on electrophoresis or spectroscopic examination, as in the case of haemoglobin.

Mention may be made of the following *physical data*, which have been taken chiefly from Theorell's publications of 1932 and 1934. The isoelectric point of myoglobin lies at pH 6.99 and that of haemoglobin at pH 6.78. The pH stability of myoglobin ranges from pH 6 to pH 13, that of haemoglobin being from pH 6 to pH 8. The maxima for light absorption are 582, 542 and 418 $m\mu$ for oxymyoglobin, and 579, 540 and 424 $m\mu$ for carboxymyoglobin. The difference from the absorption of haemoglobin is extremely small, and the α band for oxymyoglobin is 582 $m\mu$, as compared to 577 $m\mu$ for oxyhaemoglobin. The differences are greatest in the carboxy compounds, the maximum for the α band being 579 $m\mu$ for carboxymyoglobin and 568 for carboxyhaemoglobin. The molecular weight — determined by Svedberg (1938) by means of ultracentrifugation — amounts to 17,200, *i.e.*, one-fourth of that of haemoglobin, which is 68,000.

The physiological *function* of myoglobin has been extensively studied by Millikan (1937, 1939); his results were in agreement with the view that it serves mainly as a store for oxygen in the muscles. The oxygen saturation curve of myoglobin and its association and dissociation reaction velocities with oxygen have also been found to be compatible with this theory (Theorell 1934, Millikan 1937, 1939).

Little is hitherto known of the *metabolism* of myoglobin. Whipple & Robscheit-Robbins (1926) injected muscle extracts into dogs; Huppert's test then showed the presence of "bile pigment" in both the serum and the urine. London *et al.* (1950) established, by means of isotope studies, that the greater part of the bilirubin in

healthy human subjects is derived from haemoglobin, but that 11 per cent is of some other origin. In their opinion, it is probable that this fraction is derived from myoglobin. Kench & Gardikas (1952) were able in *in vitro* experiments to convert myoglobin into "bile pigment". Meldolesi *et al.* (1939) and Meldolesi (1950) stated that, in patients with muscular dystrophy, they found large quantities of a stercobilin-like substance in the faeces. They interpreted this finding as evidence that this substance — which they named myobilin — is a breakdown product of myoglobin, and that the quantity excreted in the faeces corresponds to the degree of muscular dystrophy. This observation could not be verified by Tyler & Perkoff (1951), who found the myobilin excretion to be the same in healthy subjects and in patients with muscular dystrophy.

Compared to other haemoproteins, myoglobin has been found to exhibit very slow incorporation of radioactive iron, a fact which probably indicates that the protohaemin of myoglobin has a long lifetime (Theorell *et al.* 1951).

The *renal clearance* of haemoglobin in the dog was determined by Monke & Yuile (1940) and that of myoglobin by Yuile & Clark (1941). They found a threshold value of 100 mg/100 ml of whole blood for haemoglobin, the corresponding value for myoglobin being slightly below 20 mg/100 ml. They also demonstrated that myoglobin is excreted 25 times more rapidly through the kidneys than is haemoglobin. The mechanism of excretion through the kidneys is regarded to be the same for both pigments. The great difference in the rate of excretion is probably to be ascribed to the difference in the size of the molecules.

3. *The Myoglobin Content of Different Muscles*

Whipple (1926) described a method for determination of the myoglobin content of the muscles after perfusion with Ringer's solution to remove the contaminating blood. It was not, however, possible to obtain reliable values with this method. This was because it could never be ensured that the specimens were actually free from haemoglobin, nor could it be ruled out that some loss of myoglobin might occur as a result of tissue oedema in the muscles following the perfusion. Moreover, Whipple's method could not be applied to biopsy specimens from human subjects.

Consequently, a great advance was made when de Duve (1948) elaborated a method for determination of the myoglobin content of the muscles by spectrophotometry. After Theorell & de Duve had succeeded in isolating myoglobin in the crystalline form from the urine of a patient with myoglobinuria (my Case 2), exact spectrophotometric data could be worked out for man, and the myoglobin content of mixtures of myoglobin and haemoglobin could also be determined. Furthermore, determinations could be made of the myoglobin content of biopsy specimens.

Using this method, Biörck (1949) made a thorough investigation of the myoglobin content of the muscles in normal and pathologic conditions. He determined the myo-

globin content as a percentage of the dry weight, and found the normal value for the abdominal muscles to be 2.55 ± 0.142 per cent, and that for the muscles of the extremities to be 2.73 ± 0.273 per cent. No statistically significant differences were found on comparisons between biopsy and autopsy specimens. Nor did he find any significant difference in this respect between males and females. Biörck, in similarity to Whipple, found anaemia to have little effect on the myoglobin content. In an investigation of secondary polycythaemia in congenital heart disease, he noted a slight decrease in the myoglobin concentration. This is in opposition to the observations of Hurtado *et al.* (1937), who found high values in polycythaemic dogs in the Andes. Biörck — like Whipple, among others — attributed his results to the lesser physical activity of patients with heart disease. Lawrie (1953) demonstrated in the rat that increased muscular activity over a 14-day period resulted in an increase in the myoglobin content, whereas it was unaffected by muscular exertion for a shorter period.

4. *Summary*

Myoglobin, like haemoglobin, belongs to the haemoproteins and has both a protoporphyrin and a globin component. The protoporphyrin component is similar in the two substances, whereas they differ with respect to the globin fraction. Spectroscopically, they exhibit only small dissimilarities. The greatest difference is found in the carboxy compounds, the band being $579\text{ m}\mu$ for myoglobin and $568\text{ m}\mu$ for haemoglobin. Myoglobin is considered to serve mainly as a store for oxygen in the muscles. Its molecular weight is only one-fourth of that of haemoglobin, which explains its considerably more rapid excretion through the kidneys.

In contrast to haemoglobin, the myoglobin content is only inappreciably affected by such conditions as anaemia and heart disease. The essential factor governing the myoglobin concentration is the physical activity of the muscles.

MYOGLOBINURIA IN DOMESTIC ANIMALS

1. *Introduction*

Whereas myoglobinuria is relatively rare in man, it appears to be considerably more common in domestic animals. In their case, it occurs in a number of conditions other than paralytic myoglobinuria, which is the form that has been most studied.

Since myoglobinuria in domestic animals can be presumed to bear some relation to the disease in man, a short survey is given in the following of the conditions in which it has been observed.

2. *Paralytic Myoglobinuria in the Horse*

As early as 1852, the first description of paralytic myoglobinuria — also known as lumbar paralysis or “Kreutzlähme” — in the horse was given by Hofer. At that time, it was generally considered that the disease corresponded to haemorrhagic nephritis in man. However, in 1873, Franck demonstrated that the colour of the urine was not due to haematuria, but was caused by what he believed to be free haemoglobin.

Already in 1884, Fröhner suggested that the “haemoglobinuria” was to be ascribed to the presence of muscle pigment in the urine. His view was not, however, generally accepted. Up to the nineteen-thirties, the colour of the urine was believed to be due to haemolyzed red blood cells. The investigations on the muscle pigment made by Camus & Pagniez early in the present century (*cf.* Chap. I) nevertheless lent support to Fröhner’s theory. In 1930, Carlström published a study of the aetiology and pathogenesis of this disease in the horse. By means of spectroscopic analyses, he demonstrated convincingly for the first time that it was actually a question of myoglobinuria. Fröhner’s view was thus substantiated.

Briefly, the manifestations of paralytic myoglobinuria are the following. From 15 minutes to one hour after the horse has started heavy work, tremor and sweating appear, and a limp develops in one or both hind legs. The front legs are less frequently affected. If the horse is allowed to rest at once, the symptoms may subside, but they more usually progress. On palpation of the affected muscles, particularly the psoas and quadriceps femoris, they are found to be hard and oedematous. In severe cases, the horse collapses on its hind legs and is unable to rise. A few hours after the beginning of the attack, the animal passes dark-brown urine, which contains

large quantities of proteins and myoglobin. The temperature varies with the severity of the attack. The incidence of the disease is the same in both sexes. In the mildest cases, recovery takes place after two or three days. In more severe attacks, death may ensue from myocarditis, uraemia, or septicaemia caused by infected decubitus sores. A relatively constant finding in the severe cases is a rise in the haemoglobin content and the red blood cell count of up to 50 per cent.

During the first 24 hours, the serum bilirubin is on the normal level. Only after two to three days can a considerable rise be found in severe cases. It may be mentioned by way of comparison that, in intravascular haemolysis in the horse, Bendixen & Carlström (1928, 1929) found a rise in the serum bilirubin already after two to four hours. The electrolyte content of the serum has been studied by, among others, Wester (1921), who noted normal values. Carlens (1927), on the contrary, found considerably raised serum potassium in association with the attacks.

Carlström found a slight rise in the serum creatine in severe cases. The non-protein nitrogen is initially within normal limits, but subsequently rises in severe attacks, although never to a particularly high level. In severe cases there may also be acidosis, with a decrease in the alkali reserve and marked dyspnoea.

The pathogenesis is not yet fully understood, but it appears unquestionable that a disturbance in carbohydrate metabolism is in some way responsible. The disease is chiefly seen in horses who resume heavy work after having been kept on a diet with a high content of easily resorbed carbohydrates during a rest period of two or three days. Attacks rarely occur after a shorter rest period, or after resting for more than two weeks.

Carlström was the first to succeed in provoking attacks, by means of a plentiful diet of sugar beets. Only some of the animals became affected, and the existence of a constitutional factor was therefore regarded as probable. Carlström expressed the view that the glycogen content of the muscles has some relation to the attacks. An argument in favour of this theory is that the disease is most common during the seasons in which the muscles have the highest glycogen content. Further evidence is afforded by the time at which the attacks occur in relation to the rest periods. After two to four days of rest, the glycogen content of the muscles has reached a maximum and subsequently starts to fall. This fact is considered to explain why the attacks seldom occur after only one day of rest, or when the rest period exceeds two weeks.

During the attacks, a considerable rise in the lactic acid content of the blood is recorded. This is interpreted by several authors as the actual cause of the muscular lesions (Hertha 1921, Carlström 1930).

In paralytic myoglobinuria, the muscles are pale, with a "fish flesh" appearance. On histologic examination, they exhibit Zenker's waxy degeneration. Inflammatory lesions are almost entirely lacking. Severe attacks result in widespread degenerative changes, which may also involve the cardiac muscles. In some cases there are renal lesions as well, with precipitation of myoglobin and fatty degeneration of the epithelium.

3. Other Forms of Myoglobinuria

So-called enzootic myoglobinuria in the horse greatly resembles paralytic myoglobinuria, but has a more chronic course (Hobmaier 1926, Minett 1935, Hutyra *et al.* 1949). The animal has difficulty in chewing and swallowing, owing to involvement of the masseter and throat muscles. After two to three days, dark-brown urine containing myoglobin is voided. The aetiology has not yet been elucidated. In some such cases, Carlström (1933) found marked lipaemia and severe fatty degeneration of the liver. Irwin & Pulsford (1951) observed extensive, localized necrosis of the liver. According to Carlström, it is a question of B₁ avitaminosis. The mortality rate is 50 to 66 per cent.

In the horse, myoglobinuria may also occur as a result of severe muscular strain, as well as in tetanus (Carlström 1933).

So-called waxy degeneration of the muscles has been observed in domestic animals, and attributed to avitaminosis. For example, it occurs in the lamb in a form known as white muscle disease or as stiff lamb disease; according to Swahn *et al.* (1948) vitamin E deficiency is responsible for its occurrence.

A similar form is found in the calf; it has been ascribed by Hjärre & Lilleengen (1936) to vitamin C deficiency, and by Vawter & Records (1947) to vitamin E deficiency.

Myoglobinuria may be present in these forms of waxy muscular degeneration, but is often lacking or is in any event not a prominent feature.

4. Summary

In domestic animals, a number of conditions are associated with waxy degeneration of the muscles and myoglobinuria. The best known form is paralytic myoglobinuria, which occurs in the horse. The attacks take place when the glycogen content of the muscles is highest. When the horse has remained at rest for several days on a high-carbohydrate diet, it is particularly liable to such attacks.

Another type of myoglobinuria is also encountered in the horse, *i.e.*, so-called enzootic myoglobinuria. In the calf and the lamb, waxy degeneration of the muscles, possibly due to various vitamin deficiencies, is sometimes accompanied by myoglobinuria.

MYOGLOBINURIA IN MAN

1. *Introduction*

Myoglobinuria has been reported in association with a number of pathologic conditions in man. Since no up-to-date, collective account has been published, a survey of the various classifications and of the clinical features in the different types of myoglobinuria is given in the following.

Apart from the large groups of traumatic myoglobinuria and Haff disease — and my 6 cases (see Part Two) — the literature contains altogether 20 cases in which, on the basis of the available data, myoglobinuria can be regarded as unquestionable or as highly probable. In 12 of them, the presence of myoglobin in the urine was verified spectroscopically.

2. *Classification of the Myoglobinurias*

Survey of the Literature

Myoglobinuria may appear in a number of disorders. Examples are blunt injuries to the muscles, high-voltage accidents, ischaemia of the muscles, localized muscular disease, myositis and muscular dystrophy. Finally, myoglobinuria has been known to occur without the existence of any of these factors.

Günther (1940) divided the myoglobinurias into two groups: (1) myositis myoglobinurica, and (2) paroxysmal myoglobinuria. In 1944, Brass gave the following, more detailed list in his classification of the myopathies:

“A. Die mit akutem ausgedehntem Zerfall von Muskelsubstanz und Hämoglobinurie einhergehenden Myopathien.

a) Die traumatischen Hämoglobinurien.

1. Die traumatischen Hämoglobinurien durch Verschüttung.
2. Traumatische Hämoglobinurien durch kurz dauernde heftige Gewalteinwirkungen auf die Muskulatur.
3. Mit Zerfall von Muskelsubstanz einhergehende Myopathien bei Kohlenoxydvergiftung.

b) Die Haffkrankheit.

c) Die kryptogenen Myoglobinurien des Menschen.

1. Die Myositis myoglobinurica (Günther).
2. Die Myoglobinurica paroxysmalis paralytica.”

According to Biörck, the myoglobinurias can be classified as follows:

1. Paroxysmal paralytic myoglobinuria:
 - a. Equine paroxysmal paralytic myoglobinuria and related diseases in other animals
 - b. Paroxysmal paralytic myoglobinuria in man
 - c. Haff disease
2. Acute myoglobulinolytic myositis:
 - a. Myositis myoglobinurica
 - b. Myoporphyrinuria (?)
3. Progressive muscular dystrophy (?)
4. Traumatic myoglobinuria:
 - a. "Crush syndrome"
 - b. High-voltage accident
 - c. Arterial occlusion with ischaemia

A further classification was suggested by Acheson & McAlpine (1953):

In man:

1. Associated with injury to skeletal muscle
 - a. The crush syndrome
 - b. Ischaemia due to vascular disease
2. Haff disease
3. Associated with a form of muscular dystrophy
4. Associated with temporary muscular weakness
5. Idiopathic

In animals:

1. Paroxysmal myoglobinuria in horses
2. Haff disease

Present Classification

Because of our incomplete knowledge of the different types of myoglobinuria, it is not feasible to classify them according to any fixed principle, such as their aetiology. The only rational alternative seems to be to list the various pathologic conditions in which myoglobinuria may occur. In addition, there are some unclassifiable cases. Consequently, I suggest the following classification:

- I. Traumatic myoglobinuria
 - a. Crush syndrome
 - b. Postural pressure
 - c. High-voltage accident
- II. Non-traumatic myoglobinuria
 - a. Arterial occlusion with ischaemia
 - b. Convulsive attacks
 - c. Myositis (myositis myoglobinurica)

- d. Haff disease
- e. Muscular dystrophy
- f. Familial paroxysmal myoglobinuria without progressive muscular dystrophy
- g. Unclassifiable cases

I. The traumatic myoglobinurias have been divided into three groups.

a. **Crush syndrome.** This denotes the clinically well-defined syndrome that has been described by Minami (1923) and by Bywaters and his co-workers (1941). It thus comprises only a certain type of injury, *i.e.*, the exposure of some part of the body to lengthy crushing, usually in a collapsed building or in similar situations.

b. **Postural pressure.** It has been shown by Günther (1921) that injury to the muscles can arise in this way.

c. **High-voltage accident.** Widespread muscular necrosis and myoglobinuria may sometimes result from electric shock.

II. The non-traumatic myoglobinurias have been divided into the following seven groups.

a. **Arterial occlusion with ischaemia.** Necrosis of the muscles accompanied by myoglobinuria may arise in non-traumatic arterial occlusion, *e.g.* arterial thrombosis.

b. **Convulsive attacks.** Myoglobinuria has been observed in one case of status epilepticus.

c. **Myositis myoglobinurica.** Cases of myositis with myoglobinuria as one of the features are referred to this group, irrespective of their aetiology.

d. **Haff disease.** This form of paroxysmal myoglobinuria occurred during two large, well-defined epidemics around the shores of Frisches Haff in East Prussia in 1924—1925 and 1932—1933.

e. **Muscular dystrophy.** In these cases, the muscular dystrophy is a primary cause of the myoglobinuria.

f. **Familial paroxysmal myoglobinuria without muscular dystrophy.** This is a hitherto unrecorded, familial form of paroxysmal myoglobinuria associated with a metabolic disturbance (p. 44 *et seq.*).

g. **Unclassifiable cases.** This group includes all those cases of non-traumatic myoglobinuria that cannot be referred to any of the preceding six groups.

Discussion

The classification of Brass has a drawback in that he makes no distinction between haemoglobinuria and myoglobinuria. Thus, he refers both crush injury and Haff disease to the haemoglobinurias. In his description of these conditions, he stresses that there is probably both myoglobinuria and haemoglobinuria.

Biörck has tentatively classified myoporphyria ("myoporphyrinuria") under the myoglobinurias. The term myoporphyria was introduced by Vanotti (1935) for some cases of acute porphyria with a pale appearance of the muscles. In his opinion, the

porphyrins had been formed by breaking down of myoglobin. Hitherto, there is no evidence that myoglobin can be broken down in the body into porphyrins. No porphyrins have been found in the urine in myoglobinuria. Clinically, the cases of so-called myoporphyrria reported have resembled acute porphyria in every respect. Consequently, it does not seem warranted to classify myoporphyrria — even if this term can be accepted — as a form of myoglobinuria.

Group 1 in Biörck's classification is denoted as paroxysmal paralytic myoglobinuria. The term "paralytic" in this connexion is taken from veterinary medicine, in which one of the names given to this condition in the horse is paralytic myoglobinuria. In most cases of paroxysmal myoglobinuria in man, it is questionable whether any paralysis in the true sense of the term is present. In the cases in which myoglobinuria has been described in association with muscular dystrophy it appears, however, as though paralysis has sometimes occurred. This condition is referred by Biörck to a special group, despite the fact that — being "paralytic" — it should belong to group 1 ("paroxysmal paralytic myoglobinuria").

Acheson & McAlpine make no definite distinction between group 4 ("associated with temporary muscular weakness") and group 5 ("idiopathic"). They referred the four cases described by Günther (1924), Paul (1924), Bywaters & Dible (1943) and Schaar *et al.* (1949) to group 5. Acheson & McAlpine wrote: "All the patients were adults, and the first attack was fatal, death being due to uraemia. There was no sign of previous wasting, nor was there a family history of muscular dystrophy." The cases reported by Günther and by Paul comprise a clinically well-defined group, denoted by earlier writers (Günther, Brass, and Biörck) as myositis myoglobinurica. The case of Bywaters & Dible differs in no respect from those described in group 4 ("associated with temporary muscular weakness"). It is evident from the history that the patient's symptoms had been present since childhood: "as a child, however, he was subject to 'growing pains'." At 17 years of age, on returning home after a long bicycle trip, he passed "black water, just like stout". The next morning, the urine was normal in colour. This occurred again three years later, after a cricket match and cycling, when he had to be brought home by car. It is apparent that he did not die of the first attack. Obviously, it cannot be ruled out that muscular dystrophy was present, and that this case should instead be placed in group 3.

My classification is not — as already stated — made on aetiologic principles. The respective groups are, however, clinically distinct entities.

The reason for which I have classified arterial occlusion with ischaemia as non-traumatic myoglobinuria — and not, as Biörck has done, as traumatic — is the following. In these cases, the cause of ischaemia is not a trauma in the true sense, but pathologic processes in the vessel wall or in the surrounding tissues. Arterial occlusion with ischaemia is most frequently the cause of muscle damage in crush injury as well; consequently, Biörck's grouping can scarcely be regarded as adequate in this respect.

The last group — unclassifiable cases — is certainly extremely heterogeneous from the aetiologic standpoint. It is probable that a closer analysis would show that several

of these cases actually belonged to one or other of the remaining groups. Moreover, it can be presumed that increased knowledge of the myoglobinurias would permit a subdivision of the last group.

3. *Different Forms of Myoglobinuria*

I. Traumatic Myoglobinuria

a. Crush Syndrome

During the bomb raids in London in 1940—1941, Bywaters and his co-workers observed a condition which they denoted as the crush syndrome and described in a series of papers.

They found that people who had been buried under beams, falling masonry or collapsed buildings exhibited, after their release from the compression, falling blood pressure, haemoconcentration and oedema of the extremities involved. Some of them passed dark-brown, highly acid urine, which gave a strongly positive reaction to the benzidine test. The sediment only rarely contained red blood cells, but mainly brown pigmented casts. Spectroscopic examination disclosed that the colour of the urine was due to the presence of myoglobin. Isosthenuria was present. Oliguria azotaemia, and hyperpotassaemia developed in some patients, and they died within a week. Autopsy showed pale, necrotic muscle, as well as tubular degeneration of the kidneys, with pigmented casts. In their original publication, Bywaters & Beall (1941) were of the opinion that they had discovered a new syndrome, but in a later paper (Bywaters *et al.* 1941) the investigations made earlier in Germany were cited.

Frankenthal (1916) gave the first account of the muscular lesions in the crush syndrome. The anatomic changes in the kidneys were first described by Hackradt (1917) and by Breadauer (1920).

Minami (1923) was the first to publish a complete description of the syndrome and to understand the pathogenetic association between the muscle necrosis and the renal lesions. He ascribed the renal damage to the pigmented casts, and considered the oliguria to be a result of occlusion of the tubules by methaemoglobin masses. He drew a parallel between crush injury and paralytic myoglobinuria in the horse, and quoted Fröhner's view — expressed as early as 1884 — that in the latter condition the urine contains muscle pigment. Minami did not make any spectroscopic analysis of the urine, nor did he seem to be entirely convinced of the validity of his hypothesis.

The first report of renal damage after peace-time accidents was given by Husfeldt & Bjering (1937). They did not, however, demonstrate any muscle changes.

Bywaters & Popiak (1942) and Bywaters & Stead (1944) attempted to produce the crush syndrome experimentally in the rabbit. Ischaemia was induced by means of a compression bandage on one or both thighs for 4 to 5 hours. Haemoconcentration developed through plasma loss into the damaged muscle region, which was the site of oedema. Azotaemia appeared, and was interpreted by the authors to be due partly to the impaired circulation but mainly to the increased tissue breakdown. Creatinuria and acidosis also de-

veloped, but there was no impairment of renal function. No myoglobinuria occurred; this was stated by the authors to depend on the low myoglobin content of the muscles in the rabbit. When they injected a solution of myoglobin into healthy rabbits, no renal damage resulted. If, on the other hand, the injection was made after removal of the compression bandage on the thigh, renal failure ensued; this also applied if the urine was acidified beforehand. Renal damage also failed to result if they injected an extract from rabbit muscle, which contains little myoglobin. The authors concluded from their experiments that "haemomyoglobin excreted in an acid urine such as occurs in the crush syndrome may play an important role in the genesis of the renal failure seen in that type of injury".

The results of Bywaters *et al.* were verified in 1952 by Perri & Gorini, who stressed that: "Renal block was only produced when crystalline myoglobin was injected into rabbits which had been kept on an acidifying diet and whose urine was of a pH lower than 6."

Montagnani *et al.* (1953) demonstrated, in experimental crush syndrome in the dog, that myoglobin is released from the muscles as soon as the circulation has started in an extremity that has been ischaemic for 4 to 7 hours. The quantity of myoglobin freed increased up to the second to fourth hour after circulation had been restored, but subsequently started to decrease. After 10 to 12 hours, practically no myoglobin could be demonstrated.

b. Postural Pressure

This group comprises three reported cases of myoglobinuria in which the injury was of such a type that it cannot be regarded as a crush injury.

1. De Langen (1946). The patient was a 37-year-old man in a concentration camp. "He had to make deep genuflexions for punishment during an hour and when he ceased with these with fatigue he was beaten with the butt-end of a rifle. Then he was thrown into a wet bunker where he was suffered to lie about 40 hours on a straw mattress half moist with urine."

When he was admitted to hospital, he had severe pain, particularly in his arms. He could not stand without support. His arms were swollen, and painful to the touch and on movement. His urine was extremely dark, but contained only a few red blood cells and granular casts. Spectroscopic analysis showed myoglobin to be present. There was also renal damage and a rise in the blood urea, which subsequently cleared up.

2. Jasiński & Brüttsch (1952). A 43-year-old man, after drinking wine and swallowing sleeping tablets, fell into a coma and lay in the woods for 2 1/2 days. When he woke, he had excruciating pain in both legs and could only stagger from one tree to the next. On admission to hospital, both lower legs were enormously swollen but the skin was intact. During the first 24 hours his urine was clear; it subsequently became dark-brown and myoglobin could be demonstrated spectroscopically. There was also renal impairment, with non-protein nitrogen of up to 252 mg/100 ml, as well as acidosis, the alkali reserve being 6.0 vol. per cent. The maximum creatine excretion was 76.2 mg/100 ml. Examination of a biopsy specimen from the calf muscle showed it to have the "fish flesh" appearance. Histologic examination showed that practically no intact muscle fibres were present and many fibres were necrotic. The patient recovered and was able to start walking after a month.

3. Touzé & Thierry (1952). A 20-year-old woman fell into a coma after an overdose of a barbiturate. The urine was "bordeaux-coloured" and contained plentiful blood pigment. The calf of the right leg was increased in volume, distended, as hard as stone and seemed to be tender on palpation; the ankle and the thigh were unaffected. In her comatose condition she had lain in such a way that the weight of her body rested on her right leg, which was bent under her. She had lain in this position for 16 hours. There was also renal impairment, and the authors interpreted the case as tubular blocking by blood pigments released during the lengthy contusion and muscular ischaemia. The patient gradually recovered.

c. High-Voltage Accident

The observation of myoglobinuria in high-voltage accidents is relatively recent. It was not until 1947 that Fischer & Rossier found that plentiful myoglobin was present in the urine after electric shock. This explained the severe renal damage, with oliguria and azotaemia, that is sometimes present after such accidents. Muscle damage consisting of Jellinek spirals and waxy degeneration in such cases was described by Jellinek as early as 1903. The doughy soft-tissue oedema which he denoted as "elektrisches Ödem" is also an expression of serious injury to the muscles.

Fischer & Rossier gave several examples of such severe muscular and renal damage. In some cases, the symptoms of renal failure appeared unexpectedly. The patients were in relatively good condition when anuria suddenly developed, together with a rise in temperature, and death took place within a few days. There was also acidosis and a rise in the non-protein nitrogen level. A rise in the haematocrit value was sometimes present as well. In such cases, the patient died even before any severe uraemia had had time to develop. Fischer & Rossier considered it probable that potassium poisoning was then the direct cause of death. In one of their cases, the histologic appearance of the muscles was characterized by streaks of normal muscle, corresponding to the borderlines of the current path, interrupted by areas of almost colourless muscle. Tubular damage was found in the kidneys.

II. Non-Traumatic Myoglobinuria

a. Arterial Occlusion with Ischaemia

Muscle injury and myoglobinuria may occur in arterial occlusion of various origin, *e.g.* in arterial thrombosis.

1. Bywaters & Stead (1945). The patient was a 63-year-old woman with bronchial carcinoma. Thrombosis developed in the femoral artery. There was renal failure, and spectroscopic analysis showed myoglobin to be present in the urine. At autopsy, the muscles were found to present the same appearance as in the crush syndrome.

Another type of ischaemic muscle damage was reported by Elek & Anderson.

2. Elek & Anderson (1953). A 41-year-old woman "fell down after a few gins and sustained minor injuries. These were treated and she was sent home and advised to stay in bed. Three days later she suddenly developed cramps in both legs." Any movement of the foot joints was difficult owing to severe pain in the calf muscles, which were hard and swollen. "Their woody consistency was similar to that felt in ischaemic contracture." Neither the popliteal, dorsalis pedis nor the posterior tibial artery could be palpated on either side. Thrombosis of the deep veins of the calf with secondary ischaemia was suspected, and a decompression operation was therefore performed. On cutting through the deep fascia of one calf, the muscles were seen to be paler than normally. Histologic examination of the muscles showed "a scattered lesion involving individual fibres, shrunken and separated from their sheaths; they stain poorly and the appearance suggests that myoglobin has diffused out from the fibres". The patient passed dark urine, which was found on spectroscopic analysis to contain myoglobin. Intravenous heparin therapy was given and the patient was discharged free from symptoms three weeks later.

b. Convulsive Attacks

This group contains only one authenticated case.

1. Iversen (1948). The patient was a 55-year-old man. After two days in status epilepticus, he passed dark-brown urine; spectroscopic analysis showed the presence of myoglobin. No porphyrins were found in the urine. Oliguria developed and the non-protein nitrogen rose to 300 mg/100 ml. During the 24 hours before he died, the urine was clear.

c. Myositis (Myositis Myoglobinurica)

Only two cases of myoglobinuria associated with myositis have been reported in the literature. In neither of them was the presence of myoglobin verified spectroscopically.

1. Günther (1924). A 54-year-old man fell ill with what appeared to be influenza; he had high fever and aching extremities. After two days, the symptoms subsided. After a further few days, he once again had fever, together with generalized weakness so that he could move only with difficulty, and swelling of the interphalangeal joints. One arm was swollen, and hurt on active movements. There was also painful swelling of the lumbar region on one side. His urine was dark-brown. There was subsequently painful swelling of the muscles. Examination of a biopsy specimen disclosed myositis; the muscles entirely lacked the normal colour and resembled frog muscle. Massive oedema then developed. The dark-brown colour of the urine was found on spectroscopic examination to be due to methaemoglobin (*cf.* p. 36). The author nevertheless considered that it was unquestionably a case of diffusion of muscle pigment. The patient died of phlegmon and bronchopneumonia. At autopsy, the muscles were seen in several places to be fairly pale-brown, with a "fish flesh" appearance.

2. Paul (1924). Fever and joint pains with an acute onset developed in a 42-year-old woman. Her urine was dark-red. Muscular pain also appeared. The strength of movement of the right arm was decreased, and the patient was unable to lift herself up in bed. Initially, spectroscopic examination of the urine showed the presence of methaemoglobin (*cf.* p. 36) and oxyhaemoglobin. At autopsy, the muscles were found to exhibit waxy degeneration, with a "fish flesh" appearance, varying in colour from a diffuse, waxy grey to pale rose. Paul stated: "Hämoglobinurie ist in dieser Gruppe nur ein Symptom." He expressed the view that the "haemoglobinuria" in this case was caused by dermatomyositis.

d. Haff Disease

If the crush syndrome and myoglobinuria resulting from high-voltage accidents are not taken into account, Haff disease is the best known form of myoglobinuria. Of the remaining non-traumatic myoglobinurias, only a few cases have been described. This does not apply to Haff disease, in view of the fact that several large epidemics have taken place.

The disease received its name from the place in which it first appeared, around the shores of Frisches Haff in East Prussia. It was found that, on the narrow strip of land which separates Frisches Haff from the Baltic, only those who fished in the former water were affected.

The first epidemic occurred in 1924—1925 and the second in 1932—1933. Only a few isolated cases appeared in the interim, and since the latter date the disease has not been observed there, with the exception of a minor outbreak in 1940. Altogether more than 1,000 persons became ill during the two large epidemics.

In 1934, an epidemic is stated to have taken place on the shores of a small lake near Onega in Russia.

In 1942—1943, an epidemic involving 11 cases was observed by Berlin (1944, 1948) near Lake Ymsen in Sweden.

The clinical features were described on the first appearance of the disease by Lentz (1925), Seeger & Tidow (1924), Rosenow & Tietz (1924), Ewig (1924) and Riedel (1925), and in the second outbreak by Assman *et al.* (1933). Zu Jeddloh (1939) also published a comprehensive survey of the investigations and findings in both epidemics.

Briefly, the clinical picture is the following. The onset is usually sudden and the illness is of short duration. According to Riedel, there is occasionally a prodromal stage, consisting of a slight dragging sensation in the muscles for a few days. As a rule, however, the attack starts abruptly with severe pain and tenderness in the calves, the lumbar region or the nape. There is limitation of movement, and within a few minutes — or less frequently a few hours — practically all the striated muscles are affected, with the usual exception of those of the head and throat. The pain and tenderness are often extremely severe and the patient can scarcely bear to be touched. He is afraid of moving his extremities on account of the pain, and therefore has the impression of being completely stiff. The muscles are nevertheless found to be normal on palpation, and the muscular tonus is also normal. Respiration is rapid and superficial, due to pain caused by the respiratory excursions. Initially, the patient cannot urinate on account of pain and tenderness in the abdominal muscles. A few hours later, dark-brown urine with a thick brown sediment is passed. The urine contains considerable proteins; quantitative determinations have shown values of 0.3 to 0.5 per cent and occasionally as high as 1.2 per cent. Meyer (1924) already stressed in her report of the first epidemic that the colour of the urine was probably due to myoglobin, and this was verified by Assman *et al.* by means of spectroscopic analyses during the second epidemic.

The temperature is generally normal and is only exceptionally subfebrile. High temperatures have never been recorded. At the beginning of the attack, the hands and feet are chilly; this is followed by sweating. There is also intense thirst. Lentz pointed out that the patients usually have a craving for food during the attacks; this was also observed during the second epidemic by Assman *et al.* After a few hours, less commonly up to 24 hours, the muscular pain subsides and the urine becomes pale. Fatigue and slight tenderness in the muscles may persist for a few days.

No enlargement of the spleen or the liver has ever been observed in this disease.

Leukocytosis is present, with an increase in the number of polymorphonuclear cells and concurrent eosinopenia. Both the erythrocyte count and the haemoglobin content of the blood show normal values during and after the attack.

In those cases in which the serum bilirubin has been determined, a normal level has been found (Assman *et al.*). No urinary bilirubin has ever been demonstrated. As far as the urobilin content of the urine is concerned, statements differ. Seeger & Tidow and Riedel found a negative reaction. Ewig, and Rosenhow & Tietz found, on the contrary, a strongly positive reaction.

An increased urinary output of creatine was demonstrated by Assman *et al.*

The total mortality during the two German epidemics was 1 per cent (13 cases), and Berlin had 2 deaths out of 11 patients. Renal failure with oliguria and azotaemia was present in all the patients who died. In some cases death occurred suddenly after only a short time.

Few histologic examinations have been made. Rosenow & Tietz found no pathologic changes on microscopic study of a biopsy specimen from the biceps muscle taken 24 hours after the onset of the attack. Kaiserling (1932), on the contrary, found Zenker's degeneration of the muscles in both biopsy and autopsy specimens. Parenchymal lesions of the kidneys, with extensive necrosis of the tubular epithelium, were demonstrated at autopsy by Knuth (1933). In Knuth's cases there were also older, inflammatory changes in the glomeruli, thus making the cases difficult to interpret.

The disease appears only extremely rarely to affect children; the youngest patient reported in the literature was 14 years old. The chief victims seem to be adult men. The sex incidence in 1924—1925 was 82.8 per cent men and 17.2 per cent women; in 1932—1933 it was 78.7 per cent men and 21.3 per cent women.

This predilection for men is, however, only apparent. The great majority of men affected were fishermen by occupation. Of the 400 men who contracted the disease, 314 were fishermen. In villages with a purely agricultural population, the morbidity in the two sexes was the same, *i.e.*, about 1 per cent. Thus, there is no definite sex preponderance.

Since it was assumed that the contact of the fishermen with the water was of pathogenic importance, a study of the morbidity in 1,000 dredger workers was made as a comparison. Only 1 per cent of them were found to have been affected. Moreover, no increased morbidity was found among seamen on the ships making regular runs in Frisches Haff.

An increased mortality rate in birds and mammals was found during both the German epidemics and that in Sweden.

Several theories have been put forward regarding the aetiology of Haff disease, but none of them has been fully authenticated. The fact nevertheless remains that no case of Haff disease has hitherto been observed in which eating of seafood shortly before the onset could be ruled out.

The view earlier held that some unknown gas was the causative factor has been abandoned. This also applies to the theory of waste products from a cellulose factory adjacent to Frisches Haff as the cause. Furthermore, it may be mentioned that no factory existed on the shores of the lake around which the epidemic reported by Berlin occurred.

Flury (1935) suggested that Haff disease is due to an acquired hypersensitivity to certain substances in the mud which are absorbed on eating large quantities of seafood. He based this hypothesis on the results of an experiment. A fisherman who had earlier had an attack of Haff disease suffered a fresh attack after the subcutaneous injection of sterile filtered water from Frisches Haff. Berlin also tested the possibility of an allergic origin by injecting extract of burbot liver intradermally into a patient

who had had the disease. The reaction was negative despite the use of extracts from the liver of three different burbot. In Berlin's cases, burbot liver was the foodstuff most suspected as the causative agent.

According to a theory put forward by Ågren (1944), the aetiology of Haff disease is similar to that of Chastek paralysis in silver foxes. Green *et al.* (1941) found that Chastek paralysis could be produced in these animals if 20 per cent of their diet consisted of carp, since this fish contains a vitamin B₁ inactivating factor. Lieck & Ågren (1944) studied the occurrence of this thiamine-inactivating factor in a number of species of Swedish fish. They found it to occur most abundantly in the carp.

There is no direct proof that the aetiology of Haff disease and of Chastek paralysis is the same. Neither muscle lesions nor myoglobinuria have been described in the latter. On the other hand, Chastek paralysis has occurred concurrently with outbreaks of both the German and the Swedish epidemics of Haff disease.

e. Muscular Dystrophy

Only six cases of myoglobinuria in muscular dystrophy are reported in the literature; one of them is my Case 6 in the present series (see p. 93), of which I have published an account together with Iggbom and Wahlgren (Hed, Iggbom & Wahlgren 1955).¹

1. Meyer-Betz (1910) was the first to describe a case of myoglobinuria (*cf.* p. 36). A 13-year-old boy had muscular dystrophy, manifested as atrophy of the shoulder muscles and pseudohypertrophy of the calf muscles. Since he was 7 years old, his urine had periodically contained "blood", being sometimes almost black. The muscular weakness had increased during the attacks. He had difficulty in getting up from the floor, was unable to put on his cap and had to walk on his toes. Improvement was noted between the attacks.

On admission to hospital, his urine was chocolate-brown with a thick, brown sediment. He had proteinuria which did not disappear entirely until three weeks later. The specific gravity of the urine was initially 1,005 to 1,010, but subsequently remained on a constant level of 1,010. His urinary output was large, on one occasion 3,500 ml/24 hours. The non-protein nitrogen was not determined. Tests for urobilin in the urine were negative. During his first week in hospital he was subfebrile, and thereafter afebrile. On admission there was leukocytosis, the W. B. C. being 20,000 with 88 per cent polymorphonuclears.

Spectroscopic examination showed the urine to contain methaemoglobin and oxyhaemoglobin (*cf.* p. 36). After six days, no "haemoglobin" could be demonstrated in the urine.

The patient exhibited a picture of muscular dystrophy of the infantile type, with paresis of the pelvic muscles and those of the back. His condition gradually improved and he was discharged after four months. He was still weak and had difficulty in managing stairs.

2. Louw & Nielsen (1944). The patient was a 10-year-old boy with muscular dystrophy manifested only as slight hypertrophy of the calf muscles. Since he was 4 years old, he had had repeated attacks of muscular pain in the legs, associated with difficulty in walking. The attacks were extremely brief, but there was residual tenderness of the calf muscles, which felt thick and hard. According to his mother, his urine contained blood during these attacks. In the course of such an attack, he was admitted to hospital. He then had severe pain in the calf muscles and was unable to walk. His urine was dark and was found on spectroscopic analysis to contain myoglobin. During the attack, the urinary output of creatine was high, the preformed creatine being 0.947 g and the total creatine 2.335 g/1,000 cc. Between the attacks, the preformed creatine was 1.20 g and the total creatine 1.19 g/1,000 cc. He recovered and was discharged free from symptoms of myoglobinuria. There were eight cases of progressive muscular dystrophy in the family. Only the males were affected, but the women transmitted the disease. The mode of inheritance was recessive sex-linked, and the onset occurred in childhood or adolescence. None of the other members of the family had exhibited myoglobinuria. The authors expressed the view that: "progressive muscular dystrophy and paralytic myoglobinuria may be different forms of the same disease, the latter representing the acute manifestation of the lesion, while progressive muscular dystrophy is the more chronic form of the disease".

¹ Since going to press, an additional case has been reported by Hipp & Shukers (1955).

3. Wissler (1948). When he was running and playing, a 6-year-old boy suddenly had pain in his legs and started to walk on the tips of his toes, "wie eine Balletteuse". Examination showed drop foot and tense calves, which were painful to the touch. A few hours later, he passed dark-brown, thick urine which spectroscopic examination showed to contain myoglobin. The myoglobinuria lasted for somewhat less than 24 hours. On admission to hospital his axillary temperature was 38.0° C; on the following day it returned to normal. The W. B. C. was 23,000 with 77.5 per cent polymorphonuclears on admission, but 48 hours later the values were normal. Tests for urobilin in the urine were negative. The serum bilirubin was 0.38 mg/100 cc. After 48 hours, there was no proteinuria. Two days after admission, the patient was found to have paresis of the trunk and arm muscles. He could not rise from a recumbent position without using his arms. After stooping, he could only rise to an erect position by successively placing his hands on his knees and thighs and pushing himself up. The paresis lasted for about a week. There was some residual rigidity of the calf muscles. A familial investigation disclosed that three of the patient's maternal uncles had "Muskelschwund"; two of them had died of this disease.

4. Kreutzer *et al.* (1948). A 39-year-old man had, since childhood, had attacks of aching and weakness in the legs on exertion; at the same time, he passed dark urine. He could provoke an attack by squatting. The muscles on the anterior aspect of the thighs then immediately became tender and contracted, and so weak that he could not stand after a minute. The painful cramp lasted for one to two hours, but the weakness persisted for about two weeks. He never had fever or any other systemic disturbances. One to two hours after beginning the exertion, the urine started to be dark and reached a maximum after 6 to 8 hours; after a further 10 hours, it once again began to be lighter. He could never provoke a fresh attack until two weeks later. He had noticed that the strength of both his arms and legs had decreased successively. He was found to have slight atrophy and paresis of the proximal muscles of the extremities, and a definite diagnosis of progressive muscular dystrophy was made.

On examination in hospital, it was found that attacks could easily be provoked in the way stated by the patient. Spectroscopic analysis showed the colour of the urine to be due to myoglobin. During an asymptomatic interval the urinary excretion of creatine was 0.250 g and of creatinine 1.26 g/24 hours. During an attack, the 24-hour output of creatine was 1.37 g and of creatinine 0.94 g. There was no change in the serum potassium, and normal values were also found for the serum content of the other electrolytes, the non-protein nitrogen and the alkali reserve, both during and between the attacks. Glucose and insulin tolerance tests and the intravenous hippuric acid test showed normal values. There was no rise in the lactic acid content of the serum during the attacks. Attempts to provoke an attack by the injection of dextrose and insulin, as well as of adrenalin, were unsuccessful. No familial investigation was made, but no known cases of muscular dystrophy existed.

5. Acheson & McAlpine (1953). A 30-year-old man had definite signs and symptoms of muscular dystrophy, which had been evident since he was 8 years old. He had three siblings; one sister had the pseudohypertrophic form of muscular dystrophy. Since about the age of 20, muscular exertion was followed after about two hours by voiding of dark-brown urine, which was shown to contain myoglobin. The discoloration persisted for up to 12 hours. During the attacks, there was a transient accentuation of the muscular weakness. During the free intervals, the creatine in the urine was 0.610 g and the creatinine 0.940 g/24 hours. During an attack, the corresponding figures were 0.980 g and 1.020 g/24 hours. The serum potassium at rest was 5.1 and 4.6 mEq./litre and after exertion 3.3 and 3.0 mEq./litre. The 24-hour output of 17-ketosteroids was high, varying from 23.0 mg to 42.8 mg. Examination of a biopsy specimen showed the following. "Two small pieces of vastus lateralis muscle were found to be composed mainly of muscle-fibres that appeared normal in calibre and general appearance. Among them were occasional grossly atrophied fibres with clumps or chains of sarcolemmal nuclei. These were not associated with cellular infiltration or any increase of the connective tissues. Several of the veins were surrounded by groups of small lymphocytes, but the vessels themselves were unaltered." The following results were obtained at electromyographic examination. "In the deltoid prolonged action-potential discharges were found in response to needle insertion and percussion, and there was an after discharge of voluntary contraction. Some of the discharges persisted for 30 seconds and more, and commenced at high frequencies (more than 200 per second). In the thenar eminence this myotonic reaction was much less marked. In the calf muscles the myotonia was scarcely detectable."

6. Hed, Iggbom & Wahlgren (1955. See p. 93).

f. Familial Paroxysmal Myoglobinuria without Muscular Dystrophy

This group comprises the three cases that I have reported earlier (Hed 1947, 1951, 1953). Reference is made to Chapters V and VI (pp. 42—85) for a detailed account and discussion of these cases.

g. Unclassifiable Cases

Twelve cases are contained in this group, including one that I have previously described (Hed 1951, 1953) and one of which I have published an account together with Larsson and Wahlgren (Hed, Larsson & Wahlgren 1955). These two patients (Cases 4 and 5) are also discussed in the present study (pp. 00—00).

1. Hittmair (1925). The patient was a 43-year-old woman. Her father had died of diabetes. Since the age of 41 she had had six attacks of severe pain, stiffness and tenderness in the arms and legs, accompanied by voiding of dark urine, which was shown by spectroscopic analysis to contain oxyhaemoglobin and methaemoglobin. No bile pigments were present in the urine. The liver was palpable two fingerbreadths below the costal margin. The attacks were associated with intense thirst and mental aberrations: "war leicht benommen und phantasierte etwas". During the attacks, there was marked muscular weakness; she could scarcely move either her arms or her legs. After about two weeks, she could be up but could only stand on tiptoe for a few minutes, after which she fell down. After a varying period, each attack was followed by complete recovery.

2. Debré *et al.* (1934). A 6-year-old girl had her first attack at 2 3/4 years old. The onset was sudden, with severe pain in the arms and legs so that she could not move them. Her temperature was 40° C and her pulse 170 beats/minute. Poliomyelitis was first suspected and serum was therefore given. She recovered after 12 days, although she could only stand and walk on tiptoe. After 16 days she was entirely asymptomatic. An identical attack occurred at the age of 3 1/2; once again she could only walk on tiptoe two weeks later. One month from the onset she had completely recovered. During the attacks, her urine was "bloody" although the sediment contained only a few red blood cells. Another typical attack occurred at the age of 6; there was transient muscular weakness but no discoloration of the urine.

3. Huber *et al.* (1938). A 4-year-old boy suddenly developed severe pain and tenderness in both legs. For one week the temperature was from 38 to 39° C and the pulse 160 beats/minute. After about 48 hours, he could only lift his heels 3 cm from the bed. His arms were unaffected. Poliomyelitis was first suspected, but lumbar puncture showed nothing pathologic. The Heller test for albumin in the urine was initially positive and the urine was "bloody", but only a few red blood cells were found in the sediment. No spectroscopic analysis was made of the urine. When he started to get up, he could only walk on tiptoe. Recovery was complete after a month.

4. Millikan (1939). The patient was a man; his age was not given. The only statement regarding the symptoms was that "they were nearly identical with those of the equine disease". The plasma potassium rose during exercise to about twice the normal concentration, "suggesting that his muscle membranes were made unusually permeable during activity". Myoglobinuria was demonstrated spectroscopically. No other data were given.

5. Bywaters & Dible (1943). A 24-year-old man had, since childhood, suffered from stiffness and muscular pain on exercise. On several such occasions he had passed "black water, just like stout". His last illness was diagnosed as acute nephritis and no spectroscopic examination of the urine was therefore made. The true conditions were disclosed only at autopsy. The kidneys then presented the typical appearance of distal tubular nephrosis. There were no signs of glomerulonephritis. The authors stated that the lesions were identical in every respect with those found in the kidney in the crush syndrome. Typical changes were also present in the muscles. "There is a marked patchy loss of pigment in many fibres . . . These fibres also show a marked tendency to fragmentation, which is not observed in the well-stained fibres. Occasional fibres are becoming vacuolated and breaking down, with an increase in muscle nuclei. Those which show this change are for the most part well haemoglobinised but are undergoing hyaline necrosis."

6. Scherwin (1945). A 38-year-old man had, for the past four to five years, had attacks of muscular pain and infiltrations, sometimes associated with the passage of dark-coloured urine; the reaction to benzidine was positive but it contained neither erythrocytes nor porphyrins. No spectroscopic examination of the urine was made. After the attacks, muscular atrophy developed.

7. Schaar *et al.* (1949). A 23-year-old man with paroxysmal myoglobinuria died of renal failure and pulmonary oedema. The presence of myoglobin in the urine was verified spectroscopically. No myoglobin was present during the six days before he died. No anamnestic or clinical data are given, but the authors stated that the history was suggestive of a familial occurrence. At autopsy, significant changes were found in the striated muscles and kidneys. With respect to the presence of pigmented casts, the authors stressed that: "The finding of these casts supports the concept that the precipitation of pigment is more likely the result of disturbed renal function rather than the cause of it."

8. Buchanan & Steiner (1951). The patient was a 4-year-old boy. At 2 1/2 years of age, he was admitted to hospital. The urine contained albumin and "blood". Weakness developed in the left arm and leg and the reflexes were lacking in all the extremities. The cerebrospinal fluid contained 5 mono-

cytes/cu.mm and 18.6 mg of protein per 100 cc. The patient was discharged four days later with a diagnosis of acute anterior poliomyelitis complicated by transitory acute nephritis. After two months he had recovered completely. Slightly less than two years later he had a fresh attack, with paralysis of practically all the striated muscles. The facial nerve was not paralyzed, but his palate was completely motionless and he had great difficulty in swallowing and in speaking. The muscular weakness spread successively until both arms and the trunk were completely paralyzed. Despite the use of a respirator, he died. Myoglobin in the urine was demonstrated spectroscopically, but no porphyrins. At autopsy, all the skeletal muscles showed evidence of severe, recent, progressive degeneration. It was characterized by a waxy degeneration with vacuolation and necrosis with liquefaction.

9. Spaet *et al.* (1954). A 23-year-old man had, as long as he could remember, had cramp in the calf and thigh muscles on exertion; it was so severe that he was scarcely able to walk. The attacks occurred only on exertion and he had noticed that his tolerance was greater if he had rested for some time beforehand. When he was 16, he noticed for the first time that his urine was dark during the attacks. Since then he had had about 50 attacks. Tests of the blood sugar, serum proteins, serum cholesterol, alkaline phosphatase, bromsulphthalein excretion, thymol turbidity and phenolsulphonphthalein excretion all showed normal values. The cephalin flocculation was 3+. The total serum bilirubin was 1.6 mg/100 cc; 0.6 mg direct and 1.0 mg indirect. The highest value recorded for the serum bilirubin was 2.2 mg/100 cc. The attacks could be provoked by exertion, and myoglobinuria could then be demonstrated spectroscopically. No creatine was present in the urine either during or between the attacks, nor were there any porphyrins. Examination of a biopsy specimen from the muscles taken during an attack showed no inflammatory or degenerative changes. After one attack, there was renal damage with anuria, but he recovered with the aid of an artificial kidney.

10. Hörman (1954). A 64-year-old man was admitted to hospital after the onset, a few hours earlier, of pain in the left calf and thigh so severe that he fainted on trying to move. Examination disclosed hepatomegaly; the liver was palpable four fingerbreadths below the costal margin. The icterus index (Meulengracht) was 19, and the non-protein nitrogen 48 mg/100 ml. On the day after admission, his urine was almost black. The Weber test for blood in the urine was 3+ and myoglobinuria was demonstrated spectroscopically. After four days the dark colour of the urine disappeared, but uraemia and anuria developed; they cleared up after 10 days. The patient died of thrombosis of the medial cerebral artery three days later. At autopsy, the kidneys exhibited the appearance of distal tubular nephrosis; the glomeruli were mainly unaffected, but on the borderlines of the renal cortex and medulla the tubules were almost entirely occluded by haemoglobin-containing agglomerations, desquamated epithelium and leukocytes. There was marked fatty degeneration of the liver. The striated muscles (rectus abdominalis) were essentially unaltered in structure, but degenerative foci were visible, with disappearance of the striation and sarcolemmal proliferation.

11. Hed (1951, 1953). See pp. 86—90.

12. Hed, Larsson & Wahlgren (1955). See pp. 90—93.

III. Discussion

It is evident from the foregoing that myoglobinuria may occur in many pathologic conditions. Of its known causes, the most common are trauma, Haff disease and muscular dystrophy. Among the traumatic forms of myoglobinuria, *postural pressure* occupies a unique position since the type of injury differs altogether from that in, for example, the crush syndrome. This is perhaps best illustrated by Touzé & Thierry's case. Their patient lay unconscious for 16 hours with her knees flexed and the weight of her body resting on her right calf. The resulting damage was confined to the muscles of the right calf. In two of the cases in this group (de Langen and Jasiński & Brütsch), exposure to cold may have played some role in the pathogenesis.

Waxy lesions of the muscles may sometimes arise in carbon monoxide poisoning. Günther (1921) described a case of carbon monoxide poisoning in which a 40-year-old man lay unconscious on his left side for 14 hours. Renal damage with oliguria and isosthenuria also developed, and the urine contained a pigment that was interpreted as haematoporphyrin. At autopsy, of which an account was published by Scharmann

(1921), waxy degeneration of the muscles was found only on the left side of the body, which had been pressed against the ground. Similar muscle lesions following carbon monoxide poisoning were described by Hedinger (1948).

It seems highly probable that the prerequisites for muscle damage in carbon monoxide poisoning are the same as in those cases in which an overdose of a sedative had been taken. In any event, the postural pressure influences the localization of the muscular injuries, even if the exposure to cold and the actual poisoning and shock play a role in their pathogenesis. Anoxaemia alone or shock may be responsible for waxy degeneration of the muscles (Adams *et al.* 1953). Similar muscle damage may also result from exposure to cold (Friedman *et al.* 1950). No authenticated case of myoglobinuria in carbon monoxide poisoning has been published. The prerequisites for the occurrence of myoglobinuria nevertheless exist, in view of the presence of waxy changes in the muscles.

In the aforementioned conditions, it is probable that indications of waxy degeneration of the muscles and myoglobinuria are often masked by the frequently alarming clinical features of the actual poisoning.

Non-traumatic arterial occlusion with ischaemia may — if it is of sufficiently long duration — also give rise to muscle injury and to associated myoglobinuria. The case described by Bywaters & Stead is to some extent similar to a condition in the horse in which thrombosis develops in the posterior segment of the aorta, or in one of its main branches, the external iliac or the hypogastric artery. On exertion, the horse may then present a picture resembling that in paralytic myoglobinuria, with paresis of the hind legs and myoglobinuria. This has been demonstrated by Carlström (1930) among others.

In the case described by Elek & Anderson, the causative mechanism is uncertain. It was, however, probably some form of ischaemia. I have therefore classified this case as non-traumatic arterial occlusion with ischaemia.

It is an established fact that changes in the tibialis anterior muscle may result from ischaemia. The first case of this type mentioned in the literature is that described by Severin (1943). Since then, numerous cases of the tibialis anterior syndrome have been reported (Horn 1945, Pearson *et al.* 1948, Hughes 1948, Phalen 1948, Carter *et al.* 1949, Tillotson & Coventry 1950). The patients have, without exception, been men; after unusual exertion, pain, swelling and tenderness developed over the tibialis anterior. At operation, necrotic lesions were found in the muscle in question. The pathogenetic mechanism is considered to be as follows. On exertion, the untrained tibialis anterior may swell considerably; according to Hughes, by up to 20 per cent of its initial volume. This muscle is enclosed between the interosseus membrane and the tibia and fibula behind it, and the fascia in front of it. Consequently, an increase in its volume may cause such high pressure that ischaemic changes may arise in the muscle. Probably, there is an indefinite borderline between the fully developed tibialis anterior syndrome and ordinary training ache. No authenticated case of myoglobinuria has been described in this syndrome. However, no systematic investigation seems to

have been made with a view to establishing the possible occurrence of myoglobinuria in these conditions. It nevertheless does not appear improbable that the ischaemia in the tibialis anterior syndrome might give rise to transient myoglobinuria. An indication that this may be so is given by a case reported by Pearson *et al.* On admission to hospital, this patient had no proteinuria; on the third day there was a strongly positive reaction to tests for protein in the urine.

Convulsive attacks are represented only by the case reported by Iversen. As an interesting parallel to this appearance of myoglobinuria in status epilepticus, it may be mentioned that myoglobinuria may occasionally be present in the horse as a complication of tetanus (Carlström 1933).

The two cases referred to the *myositis (myositis myoglobinurica)* group resemble each other clinically, although the histologic appearance differed somewhat. Günther regarded his case as an acute myositis, and Paul interpreted his case as dermatomyositis. In the former case, there were also inflammatory processes, whereas in the latter the lesions were more of a degenerative nature. Both reports were published in 1924, and it is strange that no similar cases have been described since then. Both Paul and Günther stated that the colour of the urine was established spectroscopically to be due to "haemoglobin". This was, however, before the spectroscopic differences between the muscle pigment and the blood pigment were generally known. In view of the marked histologic changes in the muscles and of their pallor, as well as of the clinical course, it is highly probable that it was, in fact, a question of myoglobinuria.

In a study of the earlier literature on polymyositis, Brass found a number of cases in which there was depigmentation of the muscles, and in which the urine was stated to be "bloody" or "dark-coloured", although the sediment did not contain any pathologic quantity of erythrocytes. Presumably, this symptom is frequently overlooked, especially as it is often transient. Myoglobinuria may be a feature of any form of myositis or other pathologic process in the muscles, provided that the breakdown of the muscle fibres occurs rapidly enough.

The *muscular dystrophy* group consists only of males, and the manifestations of dystrophy appeared already in early childhood.

Meyer-Betz (1910) stated that spectroscopic analysis had shown the presence of methaemoglobin and oxyhaemoglobin in the urine in his case. As in the investigation of Paul and of Günther, this observation was made before the spectroscopic dissimilarities between myoglobin and haemoglobin had become common knowledge. It appears almost unquestionable that Meyer-Betz's patient had myoglobinuria, and this has generally been accepted in the literature as the first reported case of the disease. In the other five cases in this group, myoglobinuria was verified spectroscopically.

A typical feature of several of these cases is that, during the attack of myoglobinuria, marked weakness developed in the proximal groups of muscles affected by the dystrophy. The cases of both Meyer-Betz and Wissler exhibited the features of advanced

muscular dystrophy during the attacks, whereas the symptoms were otherwise only extremely slight. In Kreutzer's case, the patient could provoke an attack only by straining the extensor muscles of the thighs. Louw & Nielsen's patient had pain and tenderness in the calves alone during the attack of myoglobinuria. Neurological examination showed slight hypertrophy of the calf muscles but no other abnormalities. Acheson & McAlpine's patient had widespread weakness and atrophy, although of relatively moderate degree. During the attacks, the generalized muscular weakness was more pronounced.

In all these cases, myoglobinuria appeared only after overexertion of the muscle groups affected. Consequently, it seems reasonable to infer that strain on dystrophic muscles results in injury to them, with associated myoglobinuria.

In only 7 of the 12 *unclassifiable cases* was the presence of myoglobin in the urine verified spectroscopically. In the other 5 the clinical features were, however, so typical that there seems every reason to regard them as cases of myoglobinuria. From the aetiological viewpoint, this group is unquestionably heterogeneous. In many of the cases, only scanty clinical data were given. It is therefore possible that some of them actually belong to one of the other groups. Several of them were originally misinterpreted. The cases of Spaet *et al.* and of Bywaters & Dible were believed to be glomerulonephritis, those of Debré *et al.* and of Huber *et al.* to be poliomyelitis, and that of Buchanan & Steiner to be both glomerulonephritis and poliomyelitis.

Of the four deaths, two were caused by tubular nephrosis (Bywaters & Dible and Schaer *et al.*), one by respiratory paralysis (Buchanan & Steiner) and one by cerebral thrombosis during convalescence from severe tubular nephrosis (Hörman).

It is possible that a number of other conditions should be included in the myoglobinurias, *e.g.* march haemoglobinuria. Some authors — for example, Whipple (1926) and de Langen (1946) — classify this syndrome as a form of myoglobinuria, whereas others regard it as one of the haemoglobinurias. de Langen reported a case in which spectroscopically verified myoglobinuria appeared after riding. The features described are not, however, identical with those characteristic of march haemoglobinuria. This condition usually arises after a long march (Feigl 1916) or running (Gilligan *et al.* 1943) and is not, as a rule, accompanied by any muscle symptoms. A comprehensive account of the syndrome has been given in a monograph by Gilligan & Blumgart (1941). Spectroscopic examinations were made in cases of march haemoglobinuria by Gilligan & Blumgart and by Lubran & Sakula (1949); they were stated to show the presence of haemoglobin in the urine.

The question of the relationship of march haemoglobinuria to the myoglobinurias can scarcely be considered as fully elucidated. It cannot be ruled out that some of the cases reported as march haemoglobinuria were, in fact, a form of myoglobinuria. In this connexion, it is interesting to recall that myoglobinuria may appear in the horse following muscular overexertion, and in army horses after strenuous rides (Carlström 1933).

4. *Summary*

After a short, critical survey of earlier classifications of the myoglobinurias, a new classification is suggested. This is followed by a survey of the different types of myoglobinuria in man, together with a review of the cases hitherto reported. In the discussion, the question is raised of a number of conditions in which myoglobinuria has not been verified, but in which it could conceivably appear, *e.g.*, the tibialis anterior syndrome, carbon monoxide poisoning and march haemoglobinuria.

PART TWO

Clinical Studies of Six Cases of
Myoglobinuria

CASE MATERIAL AND METHODS

1. *Introduction*

A brief account is given in the following of the case material on which the present studies of myoglobinuria were based. In addition to the customary physical examinations and laboratory tests, a number of special investigations were made; the techniques used are presented in the subsequent section.

2. *Case Material*

The case material comprised six patients with myoglobinuria. In four of the cases, I had the patients under observation in hospital on several occasions and examined them personally. In the other two cases, the records and other relevant information were kindly placed at my disposal by colleagues.

TABLE 1

Case	Sex	Present age yrs	Age at first attack yrs	Type of myoglobinuria	Comments
1	M	30	14	Familial	These 3 patients are brothers
2	M	29	16		
3	M	35	20		
4	M	40	31	Unclassifiable	
5	M	Dead	50	Unclassifiable	Died, aged 53 yrs, during an attack of myoglobinuria
6	M	13	12	Combined with muscular dystrophy	

TABLE 1. The case material.

It is seen from Table 1 that all the patients were males. Five of them were adults, and in these cases the symptoms did not make their first appearance until soon after puberty or in adult age. The remaining patient was a 13-year-old boy; his first attack of myoglobinuria occurred when he was 12 years old.

At the time of writing, five of the patients are alive and in good health, whereas one died during an attack of myoglobinuria.

The duration of the disease, counted from the first presumptive attack up to March 1, 1955 (or until death), ranged from 15 years to 1 year.

The observation period, counted from the date on which the diagnosis was made up to the time of writing, ranged from 10 years to 1 year.

According to the classification given on page 00, three of the patients have been referred to the familial paroxysmal myoglobinuria group (Chaps. V and VI). Two of the patients have been placed in the group of unclassifiable cases, and one has been interpreted as myoglobinuria associated with muscular dystrophy (Chap. VII).

3. *Methods*

General Methods

All the patients were investigated in hospital during one or several attacks. With the exception of Case 5, thorough clinical studies, including routine laboratory tests, were also made during one or more asymptomatic intervals.

In Cases 1—4, the following additional investigations were made: roentgenologic examinations, electrocardiographic, electroencephalographic and electromyographic recordings, and tracer tests with radioactive iodine. In Cases 5 and 6, only some of these additional investigations were made.

Special Techniques

The *myoglobin content of the muscles* was determined according to de Duve (1948).

Determinations of the *urinary output of 17-ketosteroids and corticosteroids* were made with the methods described by Birke & Plantin (1954) and Plantin & Birke (1954).

The *serum content of protein-bound iodine* was determined according to Barker *et al.* (1951); 4—8 γ per cent was taken as the normal value.

Examinations of the *autopsy specimens* (Case 5) and of the *biopsy specimens* from the liver (Cases 1, 2 and 4) and the muscles (Cases 1, 3, 4 and 6) were made with the usual histologic techniques. They included the following staining methods: van Gieson, Ehrlich's haematoxylin and eosin, and Best's glycogen.

The *biopsy specimens from the liver* were taken with a Vim-Silverman needle.

The *creatine and creatinine content of the urine* were determined according to Folin (1904). During the time the urine was collected, the patients were given a "creatine-free" diet, *i.e.*, a diet devoid of fish and meat. Determinations were made both of the spontaneous 24-hour output of creatine and creatinine, and of the output of these substances after the oral administration of 1 g of creatine.

The *bilirubin tolerance* test was performed with the methods of von Bergman (1927) and Eilbott (1927) as follows. After determination of the fasting serum bilirubin value, 0.05 g of bilirubin was injected intravenously. The serum content of bilirubin was

then determined after 3 minutes and 4 hours, respectively. The percentage of bilirubin retained was then calculated from these data.

Quantitative urinary urobilin determinations were made by means of Schlesinger's reaction on different dilutions of the urine. The values recorded are the dilutions between which the fluorescence ceased.

The *serum uric acid* content was determined according to the technique of Praetorius.

The *electrophoretic analyses of the serum* were performed with the method of Antweiler (1952).

In the *glucose tolerance tests*, the patients were given 1 g of glucose per kg of body weight by mouth. The blood sugar was determined in the capillary blood according to Hagedorn *et al.* (1935). Determinations were made of the fasting blood sugar level and of the level 30, 45, 60, 90, 120, 150 and 180 minutes after the intake of glucose.

In the *insulin tolerance tests*, 0.1 international units of insulin Vitrum per kg of body weight were injected intravenously, and the blood sugar level determined 15, 30, 45, 60, 90 and 120 minutes later.

In the *adrenalin tolerance tests*, 0.014 mg of adrenalin per kg of body weight were injected intramuscularly, and the blood sugar level determined after 15, 30, 45, 90, 120, 150 and 180 minutes.

The *low-carbohydrate diet* given during certain experiments consisted of meat, pork, fish, liver, lobster, eggs, butter, margarine, salad, cucumber, spinach, mushrooms, asparagus, tomatoes, brussel sprouts, cauliflower and leeks. The following foodstuffs were omitted from the diet: sugar, bread and all farinaceous dishes, potatoes and milk. Using the foodstuffs listed, it was possible to compose a diet satisfactory with respect to both taste and caloric content.

The methods used for the remainder of the laboratory tests were those given in "Kliniska Laborationsmetoder" by Greta Hammarsten, 2nd Ed., Stockholm 1955.

THREE CASES OF FAMILIAL PAROXYSMAL MYOGLOBINURIA WITHOUT MUSCULAR DYSTROPHY

1. *Introduction*

No accounts of the familial occurrence of paroxysmal myoglobinuria are found in the literature. For the past 10 years I have, however, had under my observation three brothers, all of whom have had repeated attacks. (Preliminary reports of the observations have already been published — Hed 1947, 1951, 1953.) These cases differ from those of other writers not only with respect to the familial occurrence, but also by the fact that this type of myoglobinuria seems to be combined with some form of metabolic disturbance. An account is given in the following of the results obtained in a systematic study of these three patients.

2. *Case Histories*

Case 1. (Case-sheet no. 7349/1954.) A man, b. Oct. 2, 1924. Railway worker.

Heredity. The patient is no. 4 of 6 siblings. The father is healthy. The mother and one maternal uncle have diabetes. One older and one younger brother (Cases 2 and 3) have the same complaint as the patient. No similar disease has been traced in any other member of the family.

Social-hygienic conditions. Married, no children. Does not drink alcohol; non-smoker. Venereal diseases denied.

Diet. Has lived on a normal diet, with plenty of milk, butter, eggs and vegetables.

Present illness. Up to about 14 years of age, the patient was entirely healthy. Since then, strenuous exercise produced aching and a feeling of stiffness in the muscles, usually beginning in the calves and spreading to the thighs and back. The symptoms invariably appeared first in the muscles under greatest strain. If, for example, he was doing hard wood chopping, they started in the arms. If he stopped working and rested as soon as the symptoms in the calves appeared, the attack was inhibited. Once the ache had spread to the muscles of the back it was too late to prevent an attack. The pain was so severe that the patient was practically incapable of movement. During the actual attack, the muscles were so tender that even a light touch on them was almost unbearable.

Intense thirst developed simultaneously; the patient tried to relieve it by frequent drinks of water ("every 10 minutes"). Although he consumed several litres of water, he was still extremely thirsty. A few hours after the beginning of the attack, he passed dark-brown, sometimes almost black urine, with a thick sediment of brown crystals.

The symptoms usually regressed after a few days. During the more severe attacks, practically all the muscles could be affected, including the intercostal muscles and those of the tongue and throat. The symptoms were then as a rule so marked that he had difficulty in managing alone, since pain was induced by the slightest movement. These severe attacks usually prevented him from working for about two weeks. He had to guard against overexertion soon after an attack, as the symptoms would otherwise recur. He also noticed that the attacks were more liable to occur if he exerted himself on

an empty stomach. Furthermore, strenuous exercise was more apt to precipitate an attack when he had an acute infection, e.g. an upper respiratory tract infection.

He had repeatedly sought medical advice for his complaints, and each time they were attributed to renal haemorrhage or glomerulonephritis.

In April 1945, the patient was called up for military service. During the first few weeks, he had no trouble, since he had only light duties. On May 5, he took part in a long march. This produced severe muscular pain, and he was able only with great difficulty to get home unaided. After a few hours, he passed dark-brown urine; the Ehrlich and Schlesinger tests were positive (1+ and 2+, respectively) and the Heller test for albumin was also positive (1+), but nothing abnormal was found in the sediment. Two days later, the S. R. was 44 mm/1 hr. He was therefore admitted to Garnisonssjukhuset in Sollefteå for investigation on May 11 and remained in hospital until May 18.

On admission, the urine was pale and clear. The Heller test and the benzidine test for blood in the urine were negative (3 specimens). Nothing abnormal was found in the sediment. Specific gravity: 1.029. The S. R. was 30 mm/1 hr on admission and 8 mm/1 hr on discharge. The total serum protein was 6.7 %, the albumin fraction being 4 % and the globulin 2.7 %. The W. R. was negative. The haemoglobin was 110 %, the R. B. C. 5,100,000, W. B. C. 5,500. Thrombocytes 209,000. On May 17, the serum bilirubin was 1.0 mg/100 ml. He was discharged free from symptoms.

On May 23, after a cross-country run and football, he had another typical attack with severe muscular pain and dark-coloured urine. He was readmitted to Garnisonssjukhuset on May 24. On admission he was almost asymptomatic. He had no difficulty in walking, but the muscles were somewhat tender. The first urine specimen was dark-brown, the benzidine test was positive (2+) and the Heller test showed traces of albumin. Only a few red blood cells and urinary casts were found in the sediment. The urine was examined by Docent B. Josephsson, who made the following report: "The pigment evidently consists of haematin or of other haematin-like blood pigment derivative. The flocculent, pigment-like precipitate present in the urine on arrival reacted strongly to benzidine when tested on a filter. The urine gave no reactions characteristic of homogentisic acid, melanin or other alkapton pigment. On spectroscopic examination, the urine showed only a general absorption beginning at about 5,000 Å and increasing downwards, as do haematin and haemin. No absorption bands characteristic of haemoglobin, methaemoglobin or similar compounds could be observed. The colour and absorption underwent no change on acidification, reduction with sodium hyposulphite or treatment with potassium ferricyanide, as do the unseparated haemoglobin derivatives. No porphyrins could be demonstrated even with fluorescence in an analysis quartz lamp. Consequently, the pigment probably consists of haematin or of closely related substances." On May 25, the serum bilirubin was 1.7 mg/100 ml and on May 29 it was 2.1 mg/100 ml. The prothrombin index (Quick) was 94 %, alkaline phosphatase (Buch) 6 units/100 ml of serum, amylase (Nörby) 0.00315 units/100 ml of serum. Hippuric acid test: 3.4 g/4 hours. The Takata test was negative.

On September 10, the patient had a fresh attack after exertion. The benzidine test was positive (2+), as was the Heller test (1+). A few red blood cells were found in the sediment. W. B. C. 12,300. The differential cell count showed 75 % segmented neutrophils, 5 % stab neutrophils, 6 % monocytes, 14 % lymphocytes and 0 % eosinophils. The blood pressure was 145/100 mm Hg. The ECG disclosed no abnormalities. At a control examination on September 17, the blood pressure was 115/75 mm Hg and the W. B. C. 5,800. On November 22, a urine specimen was analyzed during an asymptomatic interval. The Heller and benzidine tests were negative, the Ehrlich test 1+ and the Schlesinger test 2+. During this interval, the urine contained no myoglobin (Prof. H. Theorell).

The patient was placed on fatigue duty, which he managed without difficulty. On December 10, he took part in a skiing competition, which was followed by an attack with severe muscular pain and voiding of dark-brown urine. Myoglobin was demonstrated on spectroscopic examination (Prof. H. Theorell).

In 1949, slight thyrotoxic symptoms appeared. The patient was therefore hospitalized at Örnköldsvik Hospital from October 12—28 and thyroidectomy was performed, the diagnosis being diffuse toxic goitre. The patient considers that, as far as the attacks of myoglobinuria are concerned, there is a 50 per cent improvement after thyroidectomy. He has nevertheless had attacks since then after strenuous exercise, but his tolerance is considerably greater than before the operation.

From April 4—16, 1952 he was treated at the Medical Department of Örnköldsvik Hospital for bilateral hilar lymphoma, joint pains and erythema nodosum of the legs. These conditions cleared up completely, and the hilar lymphomas were not visible roentgenologically six months later. Since then, he has been healthy apart from the attacks of myoglobinuria. He has not, however, had any attack since 1953, owing to the fact that he ceased to take part in sports after his marriage.

On May 3, 1954 he was admitted to Medical Department IV of Södersjukhuset for investigation of the myoglobinuria. The results were as follows. *General condition*: no systemic disturbances. No cyanosis or dyspnoea. No oedema. *Throat and oral cavity*: nothing abnormal. *Thyroid*: healed thyroidectomy scar; no palpable thyroid enlargement. *Heart*: sounds pure, rhythm normal. *Blood pressure*: 120/70 mm Hg. *Lungs*: no dullness. Breath sounds normal. No rales. *Abdomen*: no rigidity or tender-

ness. No pathological resistance palpable. Liver and spleen impalpable. *Reflexes*: pupillary, patellar and Achilles reflexes normal. Arm reflexes normal. Babinski's sign negative bilaterally. No pareses. Strength of movement normal throughout. Rose from recumbent to sitting position without difficulty; lifted his head from the pillow easily. Volar and dorsal flexion of the feet, flexion and extension of the knee joints and movements of the hip joints normal. Volar and dorsal flexion of the hands, clenching of the fists, flexion and extension of the elbow joints and movements of the shoulder joints normal. No winging of the scapulae. No muscular atrophy or hypertrophy. No myotonic or myasthenic reactions. Muscular tonus normal. No neck rigidity. Lasègue's sign negative bilaterally. Fingernose and knee-heel tests normal. Diadochokinesia normal. No nystagmus. Romberg test negative. Gait normal. Superficial sensation (tested with cotton-wool and by pin-pricks): nothing abnormal. Deep sensation (thumb and big toe tested): normal.

Blood tests: haemoglobin 13.9 g/100 ml of blood. R. B. C. 4,600,000. W. B. C. 5,600. Differential cell count: 59 % segmented neutrophils, 2 % basophils, 3 % eosinophils, 32 % lymphocytes and 4 % monocytes. Thrombocytes 160,000. Reticulocytes 0.7 % and 0.8 %. Haematocrit 42 %. S. R. 6 mm/1 hr. W. R. negative. Total serum proteins 7.0 %. Electrophoresis: albumin + α_1 globulin 62 %, α_2 globulin 9 %, β globulin 16 %, γ globulin 13 %. Uric acid 4.8 mg/100 ml. Total serum lipoids 1.02 %.

Urinalyses: tests for albumin and reducing substance negative; nothing pathological in the sediment. Bile pigments: Bouma's and Hay's tests negative. Traces of coproporphyrin; no uroporphyrin.

Roentgenologic examinations: nothing pathological in the lungs, trachea, or superior part of the oesophagus. No enlargement of the thyroid gland or thymus.

The *electrocardiogram* showed nothing abnormal.

Ophthalmologic examination (Dr. H. Runström, Örnköldsvik Hospital) in January 1955 showed normal visual acuity and nothing pathologic in the media or fundi.

Case 2. (Case-sheet no. 7351/1954.) A man, b. March 2, 1926. Factory worker.

Heredity. See Case 1. The patient is a younger brother of Case 1.

Social-hygienic conditions. Married, no children. Does not drink alcohol; non-smoker. Venereal diseases denied.

Diet. Has lived on a normal diet, with plenty of milk, butter, eggs and vegetables.

Present illness. With respect to the myoglobinuria, the manifestations are in every detail the same as in Case 1, but have been more troublesome. Thus, the attacks occurred after considerably less exertion and were also more severe. When younger, he was a keen athlete. After ice-hockey matches, he sometimes had to be carried home, although he could usually play until the end of the match before the symptoms appeared. At times he had two attacks of myoglobinuria in one week, but generally recovered completely after a few days. In 1942, he was hospitalized for his complaint, which was diagnosed as acute nephritis.

On May 31, 1946 the patient was admitted to Garnisonssjukhuset in Sollefteå for investigation. He was then entirely free from symptoms. Examination showed the following. *General condition*: no systemic disturbances. No cyanosis or dyspnea. No oedema. *Throat*: nothing pathological. *Heart*: sounds pure, rhythm normal. *Blood pressure*: 115/75 mm Hg. *Lungs*: no dullness. Breath sounds normal. No rales. *Abdomen*: no rigidity or tenderness. No pathological resistance palpable. Liver and spleen impalpable. *Reflexes*: pupillary, patellar and Achilles reflexes normal. Abdominal reflexes normal. Arm reflexes normal. Babinski's sign negative bilaterally. *Urinalyses*: no albumin or reducing substance. Nothing pathological in the sediment. Bile pigments in the urine: Harrison's, Hay's and Hammarsten's tests negative. Iodine test negative. The Schlesinger test in the urine ranged from 2+ to 3+. Tests for porphyrins in the urine during asymptomatic interval: no uroporphyrin, no coproporphyrin. Tests during myoglobinuria attack: traces of uroporphyrin, no coproporphyrin.

Blood tests during asymptomatic interval: haemoglobin 94 %. R. B. C. 5,100,000. W. B. C. 6,300. Differential cell count: 50 % segmented neutrophils, 7 % stab neutrophils, 41 % lymphocytes, 0 % eosinophils, 2 % monocytes. Reticulocytes 0.2 %. The S. R. was 1 mm/1 hr. The icterus index (Meulengracht) was 4. Phosphatase (Buch) 5.6 units/100 ml of serum. Prothrombin index (Quick) 100 %. Amylase (Nørby) 0.00420 units/100 ml of serum. Serum calcium 10.6 mg/100 ml. Phosphorus 3.8 mg/100 ml. Takata test negative. — During the stay in hospital, the fasting blood sugar ranged from 98 to 133 mg/100 ml.

At 5 p.m. on June 2, a low-carbohydrate diet was instituted, in order to induce an attack of myoglobinuria. The notes in the case-sheet (no. 606/1946) were as follows:

June 5. 5 a.m. Yesterday evening, the patient felt tired and nauseated. He went to sleep but woke at 2 a.m. with considerable aches in his arms and legs. Respiratory embarrassment gradually supervened; there was nostril breathing and he used the scalenus muscles. He seemed to make deliberate attempts to keep his chest still owing to pain on breathing. He stated that he not only had pain, but

that he was unable to inspire to the full extent. There was no cyanosis but he seemed to be in considerable distress. His temperature was 39.3° C and his pulse 120. Heart action normal.

June 5. 8 a.m. The patient's respiration is still superficial, the respiratory excursions are extremely small, and he seems to try to keep his chest still on account of pain. He has conspicuous nostril breathing and uses the scalenus muscles. No suggestion of cyanosis. Heart: tachycardia. He is very lethargic, completely apathetic and indifferent as to whether he lives or dies. Unable to move his legs at all owing to pain, but can lift his arms 2 dm from the bed. The patellar and arm reflexes are weak but can be elicited on both sides. The Achilles and abdominal reflexes are normal. Babinski's sign negative bilaterally. Superficial and deep sensation normal. At about 10 a.m. the patient passed 260 ml of dark-brown urine. He was still extremely lethargic and could only say a few words at a time. He had difficulty in chewing and could therefore only take liquid food.

June 6. The patient had an occasional hour's sleep during the night. His pulse was irregular; on one occasion it was 44 and on another 120. He had two sudden attacks with cold sweating and bradycardia. Examination at 7.30 a.m. Heart: tachycardia but nothing else abnormal. Blood pressure: 150/100 mm Hg. General condition unchanged. The patient states that when he closes his eyes, he sees peculiar animals and objects which disappear when his eyes are open.

June 7. Respiratory difficulties unchanged. The patient is still unable to lift his legs from the bed, but can bend his knees to about right angles. Is able to move his arms practically unhindered although it causes pain. He seems to be in less distress and is no longer so lethargic and apathetic. Heart: still tachycardia. He states that he continues to see masses of peculiar objects when his eyes are closed.

June 8. The patient is still extremely tired but can move his extremities, although the strength is very poor. His respiration is still superficial. No disturbances in the reflexes. Sensation normal. The urine is paler.

June 9. No muscular pain; unhampered respiration. Urine pale.

June 10. The patient is still able to take fluids only; he states that he has difficulty in swallowing. No paresis of the palate. Earlier attacks have also been associated with swallowing difficulties.

June 14. His strength has gradually increased and he is now able to walk about unhindered. Swallowing greatly improved but he still has difficulty with coarse food.

Blood tests during and after induced myoglobinuria attack: *June 4*, icterus index (Meulengracht) 17, serum bilirubin 2.1 mg/100 ml. *June 5*, haemoglobin 96 %. R. B. C. 5,450,000. W. B. C. 16,700. Differential cell count: 78 % segmented neutrophils, 10 % stab neutrophils, 0 % eosinophils, 3 % monocytes, 9 % lymphocytes. Reticulocytes 0.3 %. *June 7*, haemoglobin 105 %. R. B. C. 4,900,000. W. B. C. 16,500. Differential cell count: 80 % segmented neutrophils, 10 % stab neutrophils, 9 % lymphocytes, 1 % monocytes. Alkali reserve 33 mM/L of plasma. Total bases 155 mEq/L. Icterus index (Meulengracht) 7.5. Serum bilirubin 0.6 mg/100 ml. *June 15*, haemoglobin 107 %. R. B. C. 5,000,000. W. B. C. 9,100. Differential cell count: 62 % segmented neutrophils, 4 % stab neutrophils, 32 % lymphocytes, 1 % eosinophils, 1 % monocytes.

After discharge from hospital on June 15, two months elapsed before he was sufficiently recovered to start work.

In 1950, the patient was admitted to the surgical department of Örnköldsvik Hospital, where thyroidectomy was performed. There was slight enlargement of the thyroid but no thyrotoxic symptoms.

Since then, he has been in good health with the exception of the attacks of myoglobinuria.

On May 3, 1954 the patient was admitted to Medical Department IV of Södersjukhuset for investigation. The results were as follows. *General condition*: no systemic disturbances. No cyanosis or dyspnoea. No oedema. *Throat and oral cavity*: nothing abnormal. *Thyroid*: healed thyroidectomy scar; no palpable thyroid enlargement. *Heart*: sounds pure, rhythm normal. *Blood pressure*: 120/70 mm Hg. *Lungs*: no dullness. Breath sounds normal. No rales. *Abdomen*: no rigidity or tenderness; no pathological resistance palpable. Liver and spleen impalpable. *Reflexes*: pupillary, patellar and Achilles reflexes normal. Arm reflexes normal. Babinski's sign negative bilaterally. No pareses. Strength of movement normal throughout. Rose from recumbent to sitting position without difficulty; lifted his head from the pillow easily. Volar and dorsal flexion of the feet, flexion and extension of the knee joints and movements of the hip joints normal. Volar and dorsal flexion of the hands, clenching of the fists, flexion and extension of the elbow joints and movements of the shoulder joints normal. No winging of the scapulae. No muscular atrophy or hypertrophy. No myotonic or myasthenic reactions. Muscular tonus normal. No neck rigidity. Lasègue's sign negative bilaterally. Finger-nose and knee-heel tests normal. Diadochokinesia normal. No nystagmus. Romberg test negative. Gait normal. Superficial sensation (tested with cotton-wool and by pin-pricks): nothing abnormal. Deep sensation (thumb and big toe tested): normal.

Blood tests: haemoglobin 12.7 g/100 ml of blood. R. B. C. 4,400,000. W. B. C. 5,000. Differential cell count: 74 % segmented neutrophils, 3 % stab neutrophils, 3 % eosinophils, 17 % lymphocytes, 3 % monocytes. Thrombocytes 140,000. Reticulocytes 0.5 % and 0.4 %. Haematocrit 41 %. S. R. 2 mm/1 hr. W. R. negative. Uric acid 5.2 mg/100 ml. Total serum lipids 0.670 %. Total serum pro-

teins 6.2 %. Electrophoresis: albumin + α_1 globulin 66 %, α_2 globulin 7 %, β globulin 12 %, γ globulin 15 %.

Urinalyses: tests for albumin and reducing substance negative. Nothing pathological in the sediment. Bile pigments: Bouma's and Hay's tests negative. Traces of coproporphyrin; no uroporphyrin.

Roentgenologic examinations: lungs: no changes in the parenchyma, hila or pleurae. Phrenicocostal sinus and diaphragm: conditions normal. No deformation or displacement of the trachea or superior part of the oesophagus. No enlargement of the thyroid gland or the thymus.

The electrocardiogram disclosed nothing pathological.

Ophthalmologic examination (Dr. H. Runström, Örnsköldsvik Hospital) in January 1955 showed normal visual acuity and nothing pathologic in the media or fundi.

Case 3. (Case-sheet no. 7350/1954). A man, b. Nov. 7, 1919. Salesman.

Heredity. See Case 1. The patient is the eldest of 6 siblings; eldest brother of Cases 1 and 2.

Social-hygienic conditions. Married, no children. Drinks alcohol only rarely; non-smoker. Venereal diseases denied.

Diet. Has lived on a normal diet, with plenty of milk, butter, eggs and vegetables.

Earlier illnesses. Scarlet fever at 11 years. Mumps at 12 years.

Present illness. Since about the age of 20, the patient has had attacks of muscular pain; the manifestations have been similar in every respect to those of his brothers. The first attack occurred after a long ski run in 1940. The second took place during his military service in 1941; he had been on strenuous duty and had played football in the afternoon. Typical symptoms appeared: muscular aches, dark-brown urine and intense thirst.

On admission to Garnissonssjukhuset in Sollefteå on May 6, 1941 his temperature was 38.2° C but it returned rapidly to normal. The Heller test for albumin in the urine was positive. The sediment contained a few red blood cells and granular casts. The non-protein nitrogen was 32 mg/100 ml. Blood pressure 145/90 mm Hg. The urinary concentration and dilution tests showed concentration to 1,021 and dilution to 1,010. He recovered completely in a few days. He was discharged from hospital with the diagnosis of chronic glomerulonephritis and was declared unfit for active service.

On June 6, 1941 he had another attack with severe muscular pains in both the arms and the legs, following strenuous exercise including football and several hours' wood chopping. There was a rise in temperature to 40.1° C with a return to normal on the following day. Four days later (June 10) he was admitted to Örnsköldsvik Hospital. The Heller test was 1+ for the first 48 hours but was subsequently negative. Only a few red blood cells and granular casts were found in the sediment. The S. R. was 11 mm/1 hr and the non-protein nitrogen 32 mm/100 ml. The test on June 17 showed isosthenuria, with concentration to 1,012 and dilution to 1,008. A new test on June 30 showed concentration to 1,016 and dilution to 1,005. Creatinine clearance: 131 ml/min.

The blood pressure was initially 150/100 mm Hg but fell to 125/80 mm Hg within a week. A test on July 7 showed concentration to 1,024 and dilution to 1,001. He was discharged on July 18 with the diagnosis of chronic glomerulonephritis. Concentration and dilution test on August 12: concentration to 1,022, dilution to 1,002. Test on November 11: concentration to 1,025, dilution to 1,001.

Since then, the patient has not been in hospital (except for investigation). He has had a number of attacks, which have occurred only after great exertion. In 1946, the urine was analyzed during an asymptomatic interval. The Heller test was negative and nothing pathological was found in the sediment. The Schlesinger test was 2+. No myoglobin could be demonstrated on spectroscopic examination of the urine (Prof. H. Theorell). The patient has otherwise been in good health. During the year prior to writing, the patient has not had an attack. He is now extremely careful and does not exert himself unduly. For example, when he is skiing and notices the onset of the symptoms, he stops immediately. He lies down and has something to eat, and then goes home by car or sleigh. He is able by this means to inhibit the attacks. When he was younger, he found it embarrassing to be forced to break off what he was doing, and for this reason his attacks were more frequent.

On May 3, 1954 the patient was admitted to Medical Department IV of Södersjukhuset for further investigation. The results were the following. *General condition*: no systemic disturbances. No cyanosis or dyspnoea. No oedema. *Throat and oral cavity*: conditions normal. *Thyroid*: no palpable enlargement. *Heart*: sounds pure, rhythm regular. *Blood pressure*: 125/75 mm Hg. *Lungs*: no dullness. Breath sounds normal. No rales. *Abdomen*: no rigidity or tenderness. No pathological resistance palpable. Liver and spleen impalpable. *Reflexes*: pupillary, patellar and Achilles reflexes normal. Arm reflexes normal. Babinski's sign negative bilaterally. No pareses. Strength of movement normal throughout. Rose from recumbent to sitting position without difficulty; lifted his head from the pillow easily. Volar and dorsal flexion of the feet, flexion and extension of the knee joints and movements of the hip joints normal. Volar and dorsal flexion of the hands, clenching of the fists, flexion and extension of the elbow joints and movements of the shoulder joints normal. No winging of the scapulae. No muscular atrophy or hypertrophy. No myotonic or myasthenic reactions. Muscular tonus normal. No neck rigidity. Lasegue's sign negative bilaterally. Finger-nose and knee-heel tests normal. Diadocho-

kinesia normal. No nystagmus. Romberg test negative. Gait normal. Superficial sensation (tested with cotton-wool and by pin-pricks): nothing abnormal. Deep sensation (thumb and big toe tested): normal.

Blood tests: haemoglobin 13.9 g/100 ml of blood. R. B. C. 4,600,000. W. B. C. 4,700. Differential cell count: 58 % segmented neutrophils, 1 % stab neutrophils, 1 % basophils. 1 % eosinophils, 38 % lymphocytes, 1 % monocytes. Reticulocytes 0.8 %. S. R. 2 mm/1 hr. W. R. negative. Uric acid 5.1 mg/100 ml. Total serum lipoids 0.810 %. Total serum protein 7.2 %. Electrophoresis: albumin + α_1 globulin 62 %, α_2 globulin 6 %, β globulin 12 %, γ globulin 20 %.

Urinalyses: Tests for albumin and reducing substance negative. Nothing pathological in the sediment. Bile pigments: Bouma's and Hay's tests negative.

Roentgenologic examinations: lungs normal. Trachea and oesophagus: conditions normal.

The *electrocardiogram* disclosed nothing pathological.

Ophthalmologic examination (Dr. H. Runström, Örnköldsvik Hospital) in January 1955 showed normal visual acuity and nothing abnormal in the media or fundi.

3. *Survey of the Symptoms*

In these three patients, the symptoms appeared for the first time between the age of 14 and 20 years. The chief complaint has been attacks of muscular pain, which occur only after strenuous exercise and never in connexion with their usual work. The muscle groups under greatest strain are invariably the first to be affected. As a rule, the discomfort starts in the calves, which feel tender and stiff, with a peculiar dragging sensation. The pain and stiffness spread to the muscles of the thighs and the lumbar region. If the patients interrupt their exercise and rest as soon as the symptoms in the calves appear, they can prevent them from spreading. Once the pain has extended to the lumbar muscles, it is too late to inhibit an attack. The pain is often so intense that they cannot move the extremities without producing a feeling "like toothache". Even the pressure of a sheet or blanket is then painful. At the height of an attack, the whole body feels "as stiff as a board". The muscles are intensely tender to palpation.

At the beginning of an attack, the patients often have difficulty in urinating. After two to eight hours, they pass urine which is dark-brown or almost black. After a few hours, up to 24, the urine regains the normal colour. Only in the most severe attacks does the discoloration persist for several days.

The attacks are associated with intense thirst, irrespective of whether or not there is fever or sweating.

Fever up to 39 to 40° C not uncommonly occurs during the attacks. As a rule, the temperature returns to normal after a few hours.

In the severe attacks, the pain may spread to practically all the striated muscles. Even the intercostal muscles and those of the tongue and throat may then be involved. After such attacks, the patients are generally unable to work for two weeks up to two months. They usually recover from the milder attacks after two to three days.

A fresh attack is considerably more apt to occur soon after one has just subsided than otherwise, and they must therefore guard against overexertion during this time. After strenuous exercise — for example, ice hockey — an attack is more liable to take place if they have not eaten properly beforehand. In addition, exertion is more likely

to give rise to an attack if they have some infection, such as an upper respiratory tract infection. No spontaneous attack has been known to occur without muscular over-exertion of some kind.

4. *Provocation of Attacks by a Low-Carbohydrate Diet*

The history showed that an attack was more liable to occur if the patients over-exerted themselves on an empty stomach or after eating too little. This was verified by the following experimental production of attacks by means of a low-carbohydrate diet.

Experiment 1: Case 2, during an asymptomatic interval.

On admission to hospital on May 31, 1946, the patient was in good condition and his temperature and pulse were normal (Fig. 1). The S. R. was 1 mm/1 hr, the icterus index (Meulengracht) 4, and the W. B. C. 6,300. After 3 days' observation, the patient was still free from symptoms. At 5 p.m. on June 2, he was given the ordinary hospital diet and thereafter a low-carbohydrate diet only. In order to eliminate the influence of muscular exertion, he was kept in bed throughout the experiment. On the evening of June 4, he felt somewhat nauseated, but fell asleep as usual, without experiencing any muscular pain which could have aroused suspicions of an incipient attack.

At 2 a.m. on June 5 (when he had been on a low-carbohydrate diet for 57 hours) he woke suddenly, complaining of intense pain and tenderness in all his muscles. When I examined him at 2.20 a.m., the findings were as follows.

There were systemic disturbances and the temperature was 39.3°C . He could not move his legs on account of pain, but was able to lift his arms 2 dm above the bed. There was respiratory distress, which was manifested as nostril breathing and use of the scalenus muscles. He seemed to make deliberate attempts to keep his chest still, owing to pain on breathing. Tachycardia was recorded (130 beats/min.) and the blood pressure was 150/100 mm Hg. The biceps, triceps and patellar reflexes were somewhat weak. The Achilles reflexes were normal, as were the superficial and deep sensation. He had difficulty in chewing and could only take fluid nourishment.

At 9.30 a.m. on the same day, he passed 260 ml of urine; it was dark-brown and had a thick crystalline sediment. Spectroscopic examination verified the presence of myoglobin. During the first 24 hours, the patient was given 30 g of sodium bicarbonate by mouth, and thereafter 15 g per 24 hours, as long as the myoglobinuria persisted. He was also given plentiful fluids, as well as large quantities of glucose both orally and parenterally.

With regard to the subsequent course of this attack, the following features are of particular interest. The initial rise in temperature was of brief duration; after $5\frac{1}{2}$ hours the temperature had returned to normal. The tachycardia, on the contrary, persisted for several days; it alternated with periods of bradycardia, the rate sometimes being as low as 44/min. When the patient was discharged, 10 days after the beginning

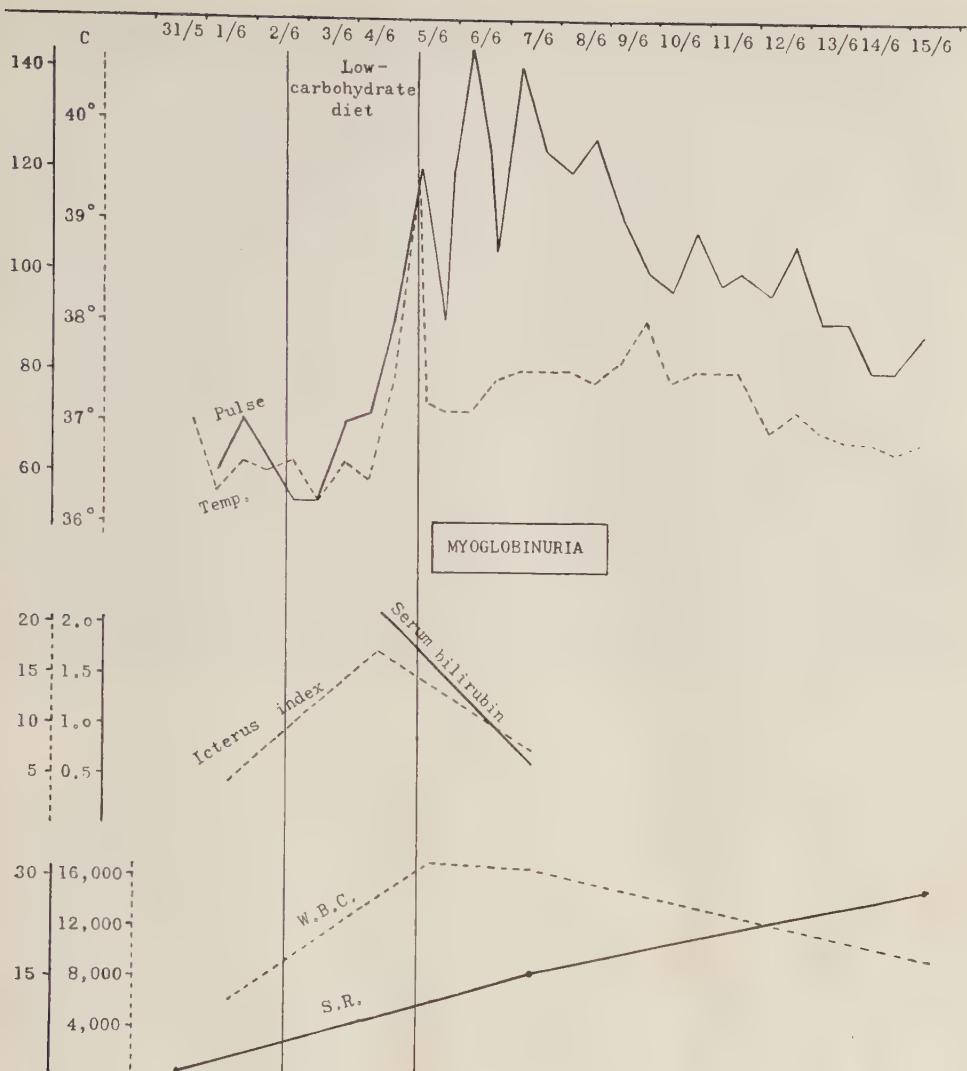


FIG. 1 Case 2. Pulse rate, temperature and some blood laboratory data in connexion with an attack of myoglobinuria provoked by a low-carbohydrate diet.

of the attack, his pulse rate was still 90/min., whereas it was normally about 60/min. The myoglobinuria persisted for about 3 days, the respiratory distress for 3 days and the dysphagia for about 10 days. The patient was able to move about freely after about a week, but only after two months was he fully recovered and fit for work. This attack was unquestionably the most severe that he or either of his brothers had ever had.

Experiment 2: Cases 1—3 during an asymptomatic interval in May 1954.

The patients were under observation for one week in hospital; during this time they were entirely free from symptoms and were able, for example, to walk 3 to 4 kilometres unhindered. They were then placed simultaneously on a low-carbohydrate diet. In view of the severe and threatening symptoms which appeared in Case 2 in connexion with experiment 1, I did not dare to keep the patients in bed. They were instead allowed to move about freely in the hospital and the grounds. This slight exertion could be expected to produce pain in the muscle groups involved and would thus give warning of an incipient attack of myoglobinuria, so that the experiment could be discontinued in good time.

The results were as follows. After about 24 hours on the low-carbohydrate diet, all three patients complained of tenderness in the muscles of the calves and stated that they had local pain in the calf and thigh muscles on walking about 100 metres. If they stopped and rested, the pain fairly soon subsided.

After a further 12 hours, Case 2 suddenly had intense pain in the calves, spreading to the thigh and lumbar muscles, after walking about 100 metres. The pain was so severe and constricting that he felt like screaming. He was unable to continue walking and had to be helped into bed by his brothers. Intense thirst developed simultaneously. The experiment was therefore ended; he was given sugar and sodium bicarbonate by mouth and kept in bed for the rest of the day. He nevertheless still had pronounced tenderness in the calf muscles on the following day, and preferred to remain in bed. Spectroscopic examination of the urine nevertheless showed no myoglobin.

The other two patients remained on the low-carbohydrate diet.

After altogether 48 hours, Case 3 had a typical attack of myoglobinuria. After walking about 100 metres, he experienced severe pain in the calves and thighs, which did not cease on resting. During the following night he could not sleep on account of the pain. He passed dark-brown urine, which was found on spectroscopic examination to contain myoglobin. During the following day, the calf muscles were still tender and aching, and the patient elected to stay in bed. In his case, the experiment was concluded after 48 hours. He was subsequently given the ordinary hospital diet with extra sugar.

In Case 1, pain and tenderness in the calf and thigh muscles appeared after 48 hours on a low-carbohydrate diet, but they were less marked than in the other two patients. The diet was therefore continued for a further 24 hours, during which the symptoms became noticeably worse. The patient consequently refused to continue the experiment. It was terminated after altogether 72 hours, and the patient then received the ordinary hospital diet. No myoglobinuria could be demonstrated.

5. Survey of the Objective Findings

Heart and Circulation

Tachycardia, with a rate of up to 130 beats/min., often occurred in the course of the attacks. In the most severe attacks, it persisted for five to six days or even longer.

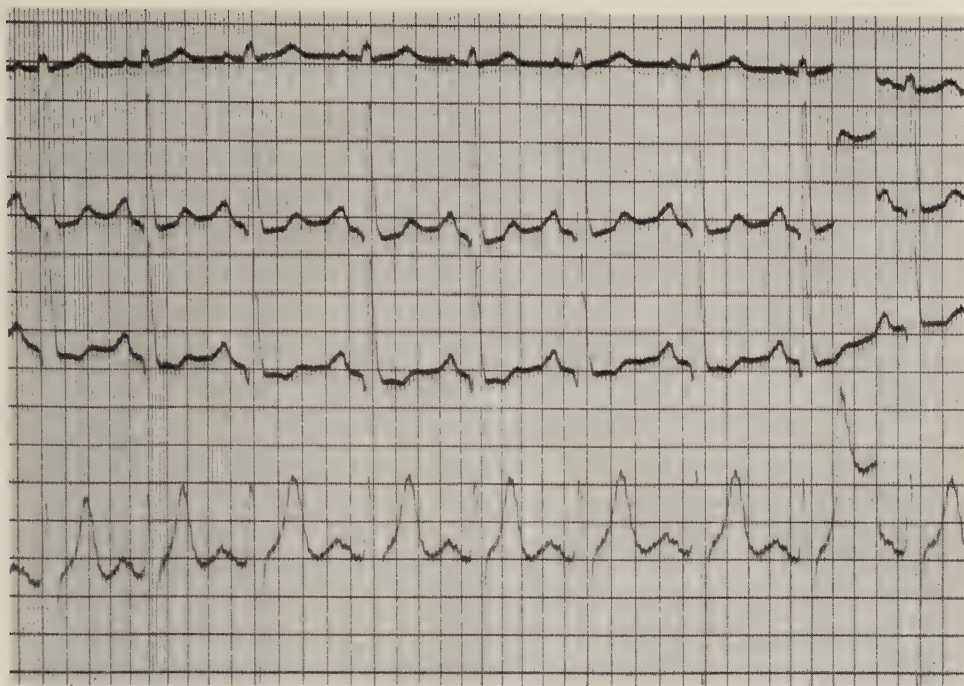


FIG. 2. Case 2. ECG recorded immediately after the onset of an attack of myoglobinuria.
Rate 130 beats/min.

An irregular heart action, with a rate varying from 44 to 130 beats/min., was observed during one attack. Despite repeated examinations, no electrocardiographic changes were found during asymptomatic intervals. In Case 2, the ECG was recorded both at the beginning of an attack and after massive myoglobinuria had been present for 48 hours. The first ECG (Fig. 2) was normal apart from tachycardia (130 beats/min.). The second showed both tachycardia (130 beats/min.) and high, peaked T waves (Fig. 3).

A slight rise in blood pressure also took place during the attacks. It was, however, of a transient nature. In Case 1, it rose from 115/75 to 145/100 mm Hg, in Case 2 from 120/75 to 150/100 mm Hg, and in Case 3 from 125/80 to 150/100 mm Hg.

Urine and Renal Function

Urine. One of the most prominent features was the dark-brown, sometimes almost black urine, with a thick sediment of brown crystals. It was established in every case by spectroscopic examination (Prof. H. Theorell) that the colour was to be attributed to the presence of myoglobin.

If plentiful sodium bicarbonate was administered during the attack, the urine became cherry-red in colour and the thick, crystalline sediment disappeared.

Proteinuria was invariably present during the actual attacks, but usually lasted for a few days only. The highest value recorded in any of the attacks was 1.1 per cent.

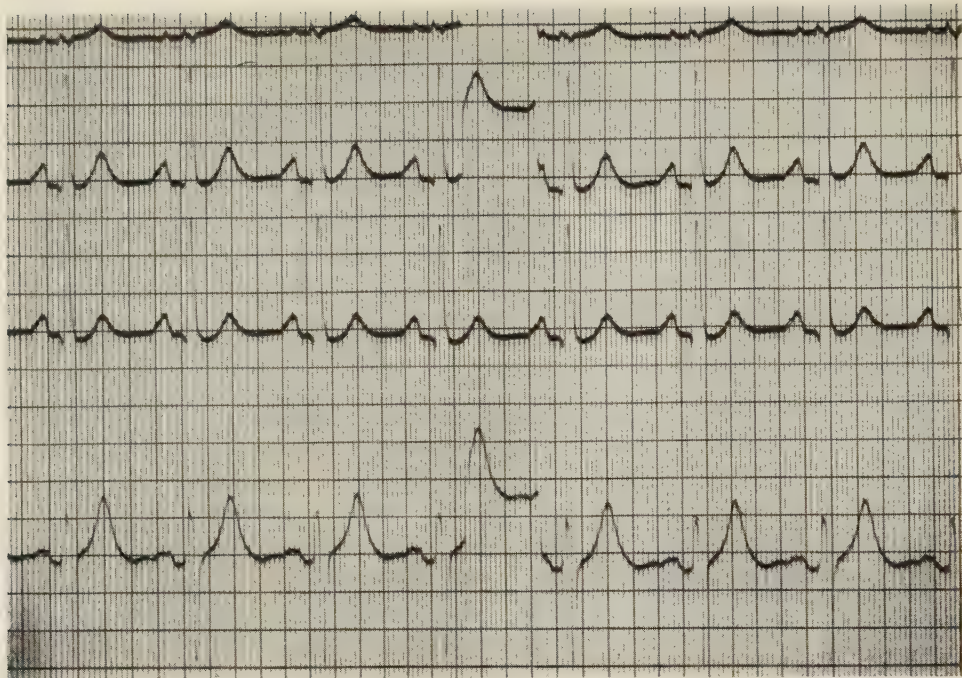


FIG. 3. Case 2. ECG recorded after 2 days' myoglobinuria. Rate 130 beats/min. The T waves are considerably higher and more peaked than in Fig. 2.

The sediment contained some granular casts, and there was microscopic haematuria with a maximum of 6 to 8 red blood cells per visual field. These formed elements usually disappeared after a few days, as a rule concurrently with the proteinuria.

Renal function. Tests of renal function were made in all three cases during asymptomatic intervals. No proteinuria was then present and nothing pathologic was found in the sediment. The creatinine clearance and non-protein nitrogen were within the normal range of variations.

Concentration and dilution tests made in May 1954 showed a good concentration ability, in all three cases to over 1,030, but a decreased dilution ability (Table 2). In Case 1, dilution was to 1,008 and 1,011, in Case 2 to 1,007 and 1,007, and in Case 3 to 1,012, 1,006 and 1,008. This impaired urinary dilution during asymptomatic intervals was found in Cases 1 and 2 as early as 1946. Dilution was then only to 1,006, whereas the figures for concentration were 1,032 and 1,025, respectively.

In 1941, Case 3 was hospitalized for two months on account of myoglobinuria. It was soon after the onset of his illness and he had only had two earlier attacks. He then underwent thorough investigations and was found to have isosthenuria, the highest concentration being 1,012 and the lowest 1,008. During the time he had isosthenuria, the creatinine clearance was normal, *i.e.*, 131 ml/min. A new test two weeks later showed that tubular function was still impaired, with concentration to

TABLE 2

Case	1941	1945	1946	1954	1954	1954
1	—	1,006 1,028	1,006 1,032	1,008 1,036	1,011 1,032	
2	—	—	1,006 1,025	1,007 1,029	1,007 1,031	—
3	1,001 1,024	—	—	1,008 1,032	1,006 1,032	1,012 1,035

TABLE 2. Concentration and dilution tests during asymptomatic intervals. Only the lowest dilution and the highest concentration are given.

1,016 and dilution to 1,005. After six weeks in hospital, the respective values were 1,024 and 1,001. A further three concentration and dilution tests were made at intervals of one month; on each occasion the figure for dilution was 1,001 and that for concentration from 1,025 to 1,026. During the entire stay in hospital, the non-protein nitrogen was on the normal level. Case 3 was also hospitalized during his first attack of myoglobinuria. The dilution was then 1,012 and the concentration 1,021.

Both Cases 1 and 2 were under observation in hospital during attacks of myoglobinuria. In both cases the output of urine and the non-protein nitrogen were normal. No concentration and dilution tests were made in these patients during attacks of myoglobinuria.

No pathologic sugar species that could have been the cause of this impaired dilution ability were found in any of the cases.

Blood and Blood Electrolytes

Numerous blood tests were made in all three cases. The following results are of particular interest.

The haemoglobin value and the red blood cell count were within the normal borders in the intervals between the attacks and were not affected by them. Between the attacks, the white blood cell count and the differential cell count were normal. During the severe attacks, there was marked leukocytosis, the W. B. C. being from 12,000 to 17,000, and neutrophilia.

The sedimentation rate was normal during the asymptomatic intervals, but rose after an attack of myoglobinuria. The highest value then recorded was 44 mm/1 hr. The S. R. usually returned to the normal level about a week after an attack. In Case 3, the S. R. and the serum fibrinogen content were determined before and after an attack induced by means of a low-carbohydrate diet. Before the attack, the S. R. was 2 mm/1 hr and the fibrinogen 0.30 per cent. After the attack, the S. R. was 10 mm/1 hr and the fibrinogen 0.47 per cent.

TABLE 3

Case	Sodium mEq./L	Potassium mEq./L	Calcium mg/100 ml	Phosphorus mg/100 ml	Serum chlorides mg/100 ml	Alkali reserve vol.%
1	145	3.7	9.6	3.2	355	66
2	147	3.4	9.8	3.3	350	69
3	145	3.5	8.8	2.8	360	61

TABLE 3. Blood electrolytes and alkali reserve. These determinations, as well as those recorded in Tables 5—13, were made during an asymptomatic interval in 1954.

The serum content of sodium, potassium, chlorides and phosphorus was determined during an asymptomatic interval. All the values were within the normal borderlines (Table 3). No determinations of the electrolyte content were made during an attack.

Glucose, Insulin and Adrenalin Tolerance

Glucose tolerance tests were performed several times (Figs. 4—6). In 1945 and 1946, both Cases 1 and 2 had paradoxical curves in tests with the oral administration of glucose. The fasting blood sugar level was high, 167 and 147 mg/100 ml, respectively, and fell after the intake of glucose. In tolerance tests made in 1954 (9 years later),

TABLE 4

Case	24-hr urinary excretion of creatine, mg		
	During asymptomatic interval	During attack	After 48 hrs low- carbohydrate diet
1	18 285 0	420	285 ¹⁾
2	25 0	1,644	273 ¹⁾
3	0 0	312 ¹⁾	312 ¹⁾

¹⁾ 12-hr output only (night urine).

TABLE 4. 24-hour urinary excretion of creatine.

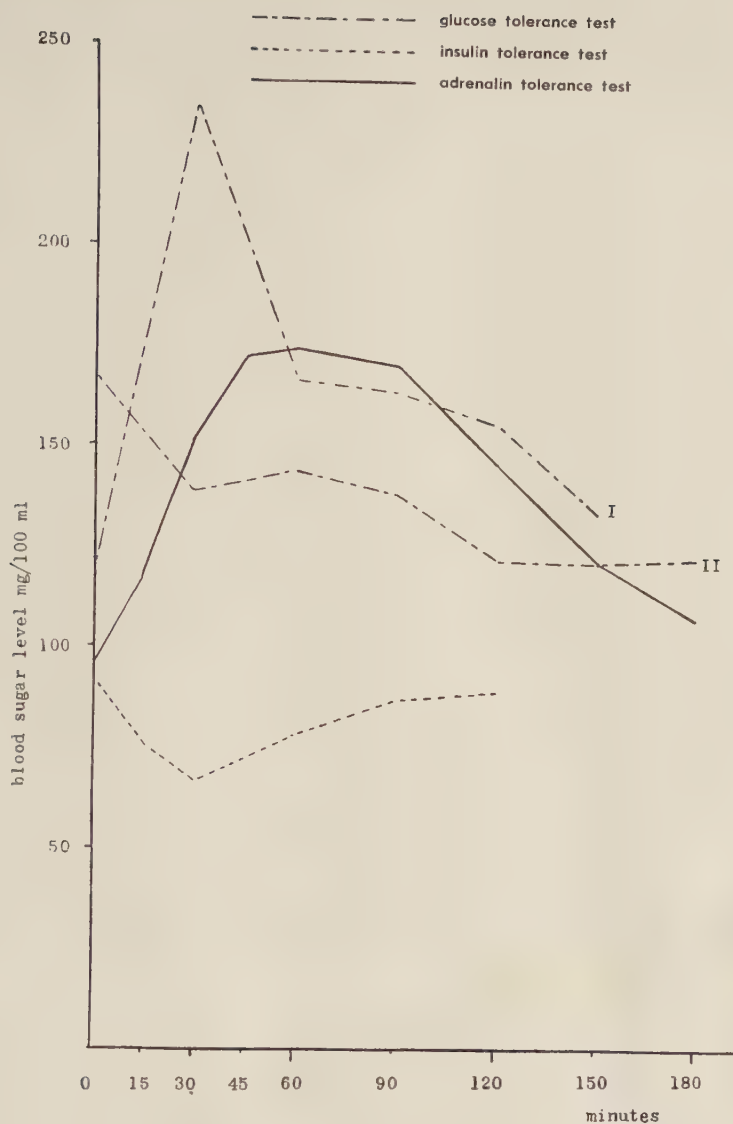


FIG. 4. Case 1. Results of glucose, insulin and adrenalin tolerance tests (1954).
I: glucose tolerance 1954. II: glucose tolerance 1945.

Case 1 had two curves of the diabetic type, whereas Case 2 exhibited a practically normal curve. The first glucose tolerance tests were made in 1954 in Case 3; two curves were then of the typical diabetic type.

Insulin tolerance tests (Figs. 4—6) showed no marked decrease in the blood sugar level in Cases 1 and 3 (Case 1: from 91 to 67 mg/100 ml; Case 3: from 98 to 78 mg/100

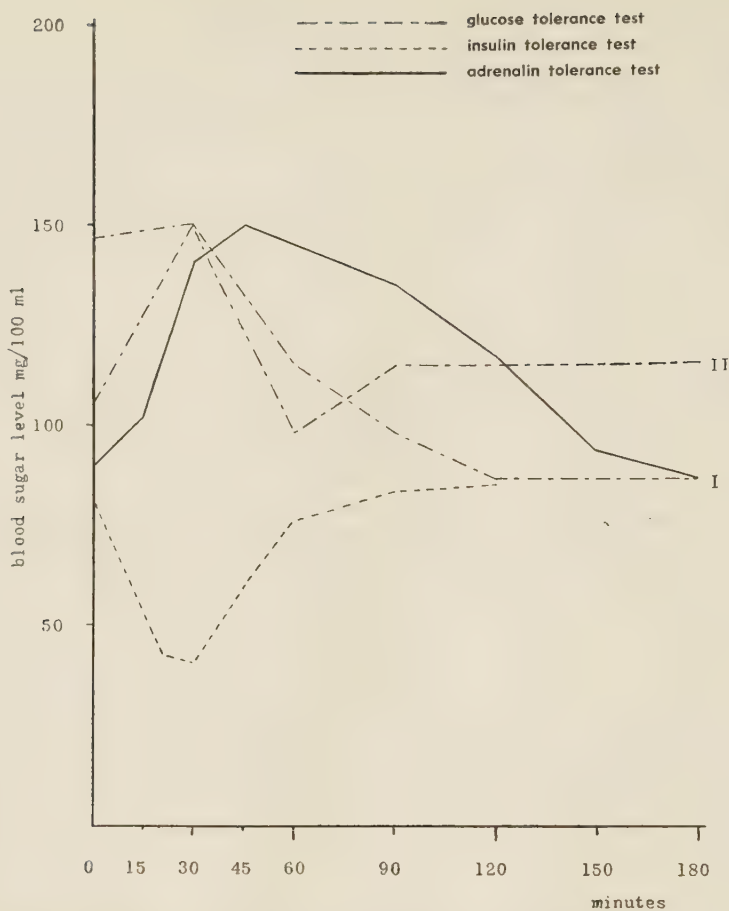


FIG. 5. Case 2. Results of glucose, insulin and adrenalin tolerance tests (1954).
I: glucose tolerance 1954. II: glucose tolerance 1946.

ml). In Case 2, on the contrary, the fall in the blood sugar level was more conspicuous, *i.e.*, from 80 to 41 mg/100 ml.

Adrenalin tolerance tests showed a completely normal reaction in the blood sugar curve in Cases 1 and 2 (Figs. 4 and 5). This test was not performed in Case 3.

Creatine and Creatinine Metabolism

The patients at times excreted small quantities of creatine in the urine during the asymptomatic intervals. The highest value recorded was 285 mg/24 hours (Table 4).

During the attempts to provoke an attack of myoglobinuria by means of a low-carbohydrate diet (experiment 2, p. 52), all three patients exhibited considerable creatinuria. Thus, Case 2 excreted 144 mg during the first 24 hours, and after 48 hours on this diet, large quantities of creatine were present in all three cases in the urine



FIG. 6. Case 3. Results of glucose and insulin tolerance tests (1954).

voided during the last 12 hours — the night urine (Table 4). (In Case 2, this was despite the fact that the experiment was terminated after 36 hours and the patient given the ordinary hospital diet with extra sugar — *cf.* p. 52.) The urine of three controls was found to contain no creatine after they had received a low-carbohydrate diet for 48 hours.

In order to obtain further information regarding the creatine metabolism during the asymptomatic intervals, tolerance tests were made on two occasions. Each of the patients was then given 1 g of creatine by mouth. The results (Table 5) showed that all three patients excreted large quantities of creatine after the tolerance tests. In Case 1, the highest value was 1,101 mg/24 hours, the corresponding figures in Cases 2 and 3 being 777 and 588 mg/24 hours, respectively. The 24-hour output of creatinine and the creatinine coefficient were also determined.

TABLE 5

Case	Urinary excretion		Creatinine coefficient
	Creatine mg/24 hrs	Creatinine mg/24 hrs	
1	779	2,652	31.2
	1,101	2,003	23.6
2	752	2,496	38.3
	777	2,412	37.1
3	315	2,704	30.5
	588	2,562	29.1

TABLE 5. Creatine tolerance tests.

The creatine output after oral administration of 1 g of creatine was also determined in 12 male controls; their age was approximately the same as that of the three patients in question. In none of these 12 controls did the output of creatine exceed 176 mg/24 hours, and in 8 of them no creatine was present in the urine (Table 6).

The highest 24-hour excretion of creatine recorded during an attack of myoglobinuria in my patients amounted to 1,644 mg (Table 4).

TABLE 6

No.	Age yrs	Creatine mg/24 hrs (urine)
1	25	0
2	32	0
3	36	0
4	43	0
5	43	0
6	40	176
7	34	0
8	35	176
9	22	73
10	26	70
11	20	0
12	20	0

TABLE 6. Creatine tolerance tests: 12 male controls.

Liver Function and Liver Biopsy

In the intervals between the attacks of myoglobinuria, a pathological increase in the urobilin content of the urine was sometimes found (Table 7), as well as a raised serum bilirubin concentration.

TABLE 7

Case	Range of dilution						
	32—64	64—128	8—16	16—32	8—16	32—64	64—128
1	32—64	64—128	8—16	16—32	8—16	32—64	64—128
2	8—16	4—8	32—64	8—16	4—8	16—32	32—64
3	16—32	32—64	8—16	8—16	8—16	16—32	64—128

TABLE 7. 24-hour urinary excretion of urobilin during one week.

The indirect van den Bergh reaction was found to be positive, whereas the direct-reading serum bilirubin reaction was negative. The highest bilirubin values recorded were 2.1 mg/100 ml of serum in Case 1, 2.1 mg/100 ml in Case 2, and 1.3 mg/100 ml in Case 3.

When Case 2 was hospitalized in 1946, the icterus index (Meulengracht) was 4 prior to the provocation test with a low-carbohydrate diet (p. 50). After this diet had been given for 36 hours, the icterus index rose to 17 and the serum bilirubin to 2.1 mg/

TABLE 8

Case		D a y						
		1	2	3	4	5	6	7
1	Bilirubin mg/100 ml	0.9	0.6	1.0	0.8	0.8	1.1	0.8
	Diet	----	----				----	----
2	Bilirubin mg/100 ml	0.9	0.5	0.9	0.7	0.9	0.6	0.3
	Diet	----	----		..++ ----	++++ ----	----	----
3	Bilirubin mg/100 ml	1.1	0.9	0.9	0.7	1.3	0.5	0.2
	Diet	----	----			++++ ----	++ ----	----

---- ordinary hospital diet

.... low-carbohydrate diet

++++ extra sugar

TABLE 8. Serum bilirubin during one week on various diets.

TABLE 9

Case	Haemolysis starts	Haemolysis complete
	% NaCl	
1	0.50	0.28
2	0.50	0.22
3	0.48	0.24

TABLE 9. Red blood cell fragility test.

100 ml. Myoglobinuria did not appear until 26 hours later (Fig. 1). As soon as the muscular pain started, large quantities of sugar were administered. Tests after the attack had lasted for three days, during which there was massive urinary excretion of myoglobin, showed a normal icterus index of 7.5 and a serum bilirubin value of 0.6 mg/100 ml.

In May 1954, when all three patients were in hospital, the serum bilirubin was slightly raised during the time they received the ordinary hospital diet. The respective figures were 1.0 mg/100 ml (Case 1), 0.9 mg/100 ml (Case 2) and 1.1 mg/100 ml (Case 3). After 48 hours on a low-carbohydrate diet, the serum bilirubin rose in Cases 1 and 3. In Case 2, the experiment had to be ended after 36 hours, since severe muscular pain developed and it was necessary to administer glucose (Table 8). In Case 2, as well as in Case 3 — who was given extra sugar at the end of the experiment, owing to severe pains in the muscles — the serum bilirubin fell to a considerably lower figure than before the experiment, when a normal diet was given. Case 1 had less marked symptoms and was therefore given no extra sugar after stopping the low-carbohydrate diet; the serum bilirubin fell only to the same level as before the experiment.

No signs of concurrent haemolysis were present. The blood counts were consistently within the normal limits. There was no increase in the reticulocyte count nor any enlargement of the spleen. The red blood cell fragility test showed normal values (Table 9). The thymol turbidity, alkaline phosphatase and Takata tests were normal, as were the electrophoresis curves of the serum protein. The galactose tolerance test performed in all three cases, as well as the hippuric acid test made in Cases 1 and 2, showed nothing pathologic (Table 10).

The bilirubin tolerance tests according to von Bergman (1927) and Eilbott (1927) showed high retention values, *i.e.*, 50 per cent in Cases 2 and 3 and 33 per cent in Case 1 (Table 11).

TABLE 10

Test	C a s e		
	1	2	3
Thymol turbidity units	1.0	1.0	0.5
Alkaline phosphatase units/100 ml serum	5.5	5.6	5.5
Takata precip. no. of tubes	0	0	0
Prothrombin index	86	96	94
Cholesterol mg/100 ml	219	188	196
Galactose tolerance excretion g	2.4	1.43	—
Fibrinogen %	0.29	0.30	0.30

TABLE 10. Liver function tests.

Histological examination of biopsy specimens from the liver (Dr. F. Wahlgren) gave the following results:

Case 1. The specimen consisted of a small slice of liver tissue, in which the acinar markings were fairly distinct. In the parenchyma, a somewhat advanced fatty degeneration was visible; it was chiefly in the form of large globules, and was mainly present in the periphery of the acini. Nothing else noteworthy was observed. In the

TABLE 11

Case	Serum bilirubin mg/100 ml			Retention %
	Fasting	After 3 mins	After 4 hrs	
1	0.7	1.6	1.0	33
2	0.7	1.7	1.2	50
3	0.4	1.2	0.8	50

TABLE 11. Bilirubin tolerance tests.

cells unaffected by fatty degeneration, small granules were present which stained red with a glycogen stain, and therefore presumably consisted of glycogen. The glycogen content was not, however, pathologically raised.

Case 2. The specimen was a small slice of liver tissue. The histologic picture was essentially normal. In specially stained sections, granules reacting positively with a glycogen stain were visible in the cells. They were not, however, present in pathological quantities.

Thyroid Function

In 1946, when Cases 1 and 2 were investigated for the first time, they showed no signs or symptoms of thyrotoxicosis. The basal metabolic rate (BMR) was then + 8 per cent in Case 1, and - 3 per cent in Case 2.

In 1949, some slight thyrotoxic symptoms appeared in Case 1; thyroidectomy was therefore performed after they had been present for about six months. The BMR was + 23 per cent pre-operatively. Microscopic examination of the thyroid gland (Prof. O. Reuterwall) showed a diffuse, so-called proliferating colloid goitre. There was fairly high, partly papillary proliferating epithelium in the follicles, and some marginal vascularity of the colloid. No distinct indications of primary toxic goitre or of adenoma. There were no grounds for suspecting malignancy. The histologic diagnosis was a diffuse, so-called proliferating colloid goitre (toxic).

Following thyroidectomy, the patient considered that there was about a 50 per cent improvement as far as the attacks of myoglobinuria were concerned.

In 1950, thyroid enlargement was diagnosed in Case 2 as well, and thyroidectomy was performed. Before operation, the BMR was - 11 per cent. Microscopic examination of the thyroid gland (Prof. O. Reuterwall) showed a diffuse colloid goitre. The structure consisted mainly of medium-sized follicles, with low cubical epithelium and fairly thick colloid. Small lymphoid foci were present. The structure was not that of a toxic goitre. The histologic diagnosis was a diffuse colloid goitre.

TABLE 12

Case	Uptake in thyroid after 24 hrs %	Urinary excretion first 24 hrs %	Protein-bound iodine γ %
1	44	49	6.5
2	48	34	4.7
3	45	47	5.7

TABLE 12. Tracer tests with radioactive iodine (0.08 m C I¹³¹ by mouth) and serum content of protein-bound iodine.

In this case, the patient noticed no improvement with regard to the attacks of myoglobinuria after thyroidectomy. In May 1954, when all three patients were hospitalized, new tests were made of the thyroid function. None of the patients exhibited any clinical signs of hyperthyrosis. Tests with radioactive iodine and protein-bound iodine showed normal values (Table 12).

Adrenocortical Function

The adrenocortical function was studied by determination of the 24-hour urinary output of 17-ketosteroids and corticosteroids, and by chromatographic separation of the 17-ketosteroids (Docent G. Birke and Civiling, L.-O. Plantin). Three determinations were made in Cases 2 and 3, and two determinations in Case 1 (Table 13).

TABLE 13

Case	17-Ketosteroids mg/24 hrs	Corticosteroids mg/24 hrs
1	12.1 8.5	8.0
2	6.5 8.3 7.0	5.9
3	6.3 13.9 11.4	9.9

TABLE 13. 24-hour urinary output of 17-ketosteroids and corticosteroids.

After separation of the main 17-ketosteroids, the microchromatograms in Cases 1 and 2 exhibited an entirely normal appearance according to the normal values for the method given by Plantin & Birke (1954). In Case 3, there was, on the contrary, a rise in the fraction in which dehydroepiandrosterone is present. In the three analyses made in this case, the quantity of dehydroepiandrosterone was 26.4, 27.9 and 26.0 per cent, respectively, of the total urinary output of 17-ketosteroids.

Neurological Examinations

Thorough neurological examinations were made both during attacks of myoglobinuria and during asymptomatic intervals. During the asymptomatic intervals, no pathological phenomena were observed. Thus, there was no paresis, atrophy or pseudohypertrophy. The reflexes and sensation were normal. No myotonic or myasthenic reactions were evoked. Electromyographic tracings from the gastrocnemius muscle showed entirely normal conditions in all three cases.

Neurological examination during mild and moderately severe attacks also failed to reveal any abnormalities. During the severe attack induced in Case 2 in 1946, the patient had difficulty in lifting his arms and legs, owing to pain. No definite pareses were, however, present. All the reflexes in the extremities were normal.

In 1954, electromyographic tracings were recorded from the gastrocnemius muscle in Case 3 during an attack of myoglobinuria, but nothing pathologic was found. In this attack, only the calf muscles were affected; they ached and were extremely tender on palpation.

During the actual attacks, the patients sometimes exhibited mental anomalies. They were often strikingly lethargic and apathetic. This applied in particular to Case 2 during a severe attack. He then had visual hallucinations, although his temperature was normal. In the intervals between the attacks, the patients' mental reactions were fully normal.

During hospitalization in 1954, electroencephalograms were recorded in all three patients during an asymptomatic interval. The results were as follows (Docent L. Kirstein).

Case 1. Bipolar recording with 21 electrodes. The patient was awake at times, and at others he was drowsy. During the periods he was awake, the tracing from postcentral regions showed a dominant activity of stable nature with a frequency of about 11/sec. and an amplitude of 30—50 μ V. This activity was symmetric and was normally blocked by visual stimulation. When the patient was drowsy, a slow activity, typical of this condition, was recorded from the entire cortex. During the periods when the patient seemed to be awake, occasional, scattered, slow potentials were recorded; they had a duration of 150—200 milliseconds and an amplitude of about 30 μ V. It could not be determined with certainty whether these potentials were to be ascribed to the fact that the patient was about to drowse off. No pathologic activity was recorded during hyperventilation. When the patient was fully awake, the tracing was completely normal.

Case 2. Bipolar recording with 21 electrodes. Postcentrally, the tracing was dominated by an activity with a frequency of 7 1/2 and 8/sec., and an amplitude of 30—50 μ V. This activity was of a stable nature and symmetric; it was normally blocked by visual stimulation. The tracing from the same regions also showed a periodically marked incidence of scattered, slow potentials with a duration of 150—250 milliseconds and an amplitude of about 30 μ V. No change was produced by hyperventilation. The tracing showed generalized pathologic activity of an unspecific nature.

Case 3. Bipolar recording with 21 electrodes. Postcentrally, the tracing exhibited a dominant activity of stable nature, with a frequency of 11/sec. and an amplitude of 30—40 μ V. The activity was symmetric and was normally blocked by visual stimulation. No pathologic activity was present. No change was produced by hyperventilation. The tracing was normal.

It may be inferred from the foregoing that Case 2 had a definitely pathologic EEG during an asymptomatic interval. No other indications of organic brain damage were found in this patient, nor was there any history of a head injury.

In the other two patients, no pathologic changes were found in the EEGs recorded during an asymptomatic interval.

Histologic and Chemical Examination of Biopsy Specimens

A specimen of the tibialis anterior muscle was taken for biopsy in Case 1 in 1946, two weeks after an attack of myoglobinuria. In Case 3, a biopsy specimen from the gastrocnemius muscle was taken in May 1954, two days after an attack. In the latter case, the specimen was divided into two parts immediately after removal. One part was taken for histologic examination and the other for determination of the myoglobin content.

The myoglobin content was found to be low, *i.e.*, only 0.68 per cent, in contrast to the normal figure of 2.73 per cent.

The results of the histologic examinations were as follows.

Case 1. (Examination by Prof. N. Gellerstedt.) No definite difference in the stainability could be noted in specimens fixed in various media. Nothing noteworthy was found in the unstained specimens. The only feature that might be denoted as pathologic in comparison with other specimens of the skeletal muscles was a generalized increase in the sarcolemmal nuclei (in cross-section specimens), as well as an apparently uneven distribution (in longitudinal sections). There was possibly a slight, diffuse increase in the fine connective tissue between the individual muscle fibres. In other respects, the striation and longitudinal fibrillation had the usual appearance, and no other definitely pathologic features were observed.

Case 3. (Examination by Prof. G. Wohlfart.) The specimen from the gastrocnemius muscle showed no definitely pathologic features. It is true that there was a slight increase in the number of nuclei in some of the muscle fibres, but this may also be observed normally. No atrophic or hypertrophic fibres or other pathologic changes were visible.

6. Discussion

The Symptoms

The degree of severity of the attacks varies appreciably, but they are invariably associated with excruciating pain and tenderness in the muscles. The feeling of stiffness — described by the patients as being “as stiff as a board” — is probably to be ascribed to their attempts to immobilize the joints, owing to the pain produced by movement. No objective explanation of this feeling can be found. Examination disclosed no infiltration or oedema of the muscles nor any increase in muscular tonus, and there was no limitation of movement in the joints.

At the beginning of an attack, the patients often have difficulty in urinating; this is probably due to pain and tenderness in the abdominal muscles. The same feature is found in Haff disease and has been explained in the same way.

Intense thirst is associated with the attacks. It is present irrespective of whether or not there is fever or sweating. Thirst is often present in Haff disease as well, in which a craving for food has also been observed. It is hard to find any explanation of this thirst, but it is a characteristic symptom of the familial form of myoglobinuria, and is a feature of practically every attack.

The attacks occur only after overexertion. According to the patients, they are more liable to be produced by exertion on an empty stomach or when they have an infection. A fresh attack is considerably more likely to occur soon after one has just subsided than otherwise, and they must therefore avoid overexertion during this time. The same observation was made by Spaet *et al.* Kreutzer *et al.* found the opposite to apply. After provocation of an attack in their patient, who had muscular dystrophy and myoglobinuria, no fresh attack could be provoked until at least two weeks had elapsed.

Provocation of Attacks by a Low-Carbohydrate Diet

Muscle strain as a precipitating factor in some cases of myoglobinuria has been demonstrated by several authors (*e.g.* Kreutzer *et al.*, Acheson & McAlpine, and Spaet *et al.*). Nothing is, however, found in the history of any of the cases earlier described to suggest that the carbohydrate content of the diet was of any consequence in this respect. Meyer-Betz was the only one to investigate whether the diet played any role in the causation of the attacks. He found no indications of any such effect in his case; he was unable to produce an attack either with a high-carbohydrate diet or with a high-protein and high-fat diet.

In experiment 1 (Case 2), the symptoms appeared abruptly and simultaneously in the whole body, in a way that the patient had never experienced previously. He had never before had an attack that was not preceded by muscular exertion, and the muscles under greatest strain had invariably been the first to be affected. By ceasing work and having something to eat, he had often been able to inhibit an attack. During the experiment he was, on the contrary, in bed and therefore strained no muscles. Consequently, he was not warned of an incipient attack by aches in any particular group of muscles, and the symptoms appeared concurrently in practically all the striated muscles. Moreover, no earlier attack had been nearly as severe.

In experiment 2 as well, a low-carbohydrate diet produced severe muscular pain in all three patients, and in Case 3 there was also myoglobinuria. It is remarkable that no urinary excretion of myoglobin occurred in Case 2, although the symptoms were the same as in a full-blown attack. Both pain in the lumbar muscles and intense thirst were present. Similar conditions — muscular involvement without myoglobinuria — may also be found in Haff disease and in lumbar paralysis in the horse.

The results of these experiments afford conclusive evidence that myoglobinuria can be provoked in my three cases by a low-carbohydrate diet. Moreover, they lend support to the assumption that these patients have some disturbance in carbohydrate metabolism.

Heart and Circulation

The most conspicuous circulatory manifestation is tachycardia. In Case 2, it persisted after the cessation of myoglobinuria. As late as 10 days after the beginning of the attack, his pulse rate was 90/min., as compared to about 60/min. before it (see Fig. 1, p. 51).

The slight rise in blood pressure associated with the attacks is obviously of no clinical importance, but it was one of the reasons for which the earlier attacks were interpreted as acute or chronic glomerulonephritis.

Urine and Renal Function

Proteinuria and the presence of casts and red blood cells in the sediment during the attacks make these cases liable to be misinterpreted as glomerulonephritis. There is, however, always a striking discrepancy between the sometimes almost black colour of the urine and the inappreciable number of red blood cells found in the sediment.

It is an established fact that renal damage with retention of urea often occurs in myoglobinuria. Renal failure in the crush syndrome has been stressed as a typical example of lower nephron nephrosis (Lucké 1946, Burch & Ray 1949). The cases described by Bywaters & Dible and by Schaar *et al.* died of uraemia in association with myoglobinuria, and at autopsy the kidneys presented the appearance typical of lower nephron nephrosis.

No severe renal damage has been observed in my cases of the familial type of myoglobinuria. Tests made a few days after an attack nevertheless showed isosthenuria, despite a normal urinary output, nothing pathologic in the sediment, non-protein nitrogen within the normal limits, normal creatinine clearance and a negative reaction to tests for protein. A few months later, no isosthenuria was found.

The inability to produce diluted urine — a feature present in all three cases on investigation in May 1954 — did not seem to exist in the early stages (Table 2, p. 55). In Case 3, the dilution test showed normal values after the third attack, not long after the onset. In Cases 1 and 2, concentration and dilution tests were not made until 4 and 6 years, respectively, after the onset of the illness; during this time they had had repeated attacks of myoglobinuria. The tests then showed decreased dilution ability. It is not improbable that this is due to impairment of tubular function, caused by the repeated injury to the tubular epithelium constituted by the attacks of myoglobinuria.

Blood and Blood Electrolytes

In the traumatic forms of myoglobinuria — the crush syndrome and high-voltage accidents — a rise in the haematocrit value is found; this also applies to paralytic myoglobinuria in the horse. The non-traumatic forms in man are not, on the contrary, associated with any increase in the red blood cell count. Nor did I find any such increase during the attacks in my cases. During the severe attacks, there was

marked leukocytosis with neutrophilia. The white blood cell count then ranged from 12,000 to 17,000. Similar observations were made by Wissler, Buchanan & Steiner and Spaet *et al.*, among others. In Case 3, the white blood cell count was normal (6,200) during a very mild attack. The highest value (16,700) was noted in Case 2 in the course of an extremely severe attack. Thus, judging by the few observations made, the degree of leukocytosis seems to be parallel to the degree of severity of the attack.

A rise in the sedimentation rate occurred after the severe attacks; the highest figure recorded was 44 mm/1 hr. In a mild attack in Case 3, a rise in the S. R. from 2 to 10 mm/1 hr was accompanied by an increase in the serum fibrinogen from 0.30 to 0.47 per cent. Fagerberg *et al.* (1941) have shown that free haemoglobin in the blood stream causes an increase in the fibrinogen content; my findings indicate that this also applies to myoglobin.

During the asymptomatic intervals, no disturbances in the electrolyte balance were found in my cases (Table 3, p. 56). During the attacks of myoglobinuria there is, on the contrary, reason to presume that there is a rise in the serum potassium, since the muscles have a high potassium content. Carlens found high values in paralytic myoglobinuria in the horse, as did Millikan in a case of myoglobinuria in man. Millikan did not, however, give any figures, nor did he state whether any clinical indications of potassium poisoning were present. He wrote: "In this case the patient's plasma potassium went up during exercise by about double the normal rise, suggesting that his muscle membranes were made unusually permeable during activity."

Acheson & McAlpine found low serum potassium values during an attack provoked by exertion. Their patient had an increased urinary excretion of adrenocortical steroids, the maximum output of 17-ketosteroids being 42.8 mg/24 hours. Consequently, the somewhat low serum potassium level during exercise might possibly, in this case, be due to an endocrine dysfunction. Kreutzer *et al.* and Spaet *et al.* found no significant difference in the serum potassium level before and after attacks produced by overexertion.

Whether a high or a low serum potassium level is found during an attack of myoglobinuria is presumably dependent partly on the stage at which the blood sample is taken, and partly on the state of renal function. If there is concurrent renal impairment with oliguria, the risk of hyperpotassaemia is imminent. In all probability, hyperpotassaemia is often the direct cause of death in the crush syndrome and in electric shock, as has been pointed out by several authors. This applies in particular when the patient dies suddenly at an early stage, before severe renal failure has had time to develop (see Case 5, p. 90). In Buchanan & Steiner's case of myoglobinuria, widespread paralysis supervened and involved the respiratory muscles; it seems probable that death was caused primarily by potassium poisoning. In the later stages of renal failure of the lower nephron nephrosis type, when the urinary output is large, the serum potassium level may be low (Callaway *et al.* 1952). When renal function is unimpaired, any hyperpotassaemia is presumably only transient, and is therefore difficult to establish by means of blood tests.

No determinations of the serum potassium were made in my three cases during an attack of myoglobinuria. However, when Case 2 had an extremely severe attack provoked by a low-carbohydrate diet, the electrocardiogram was recorded both immediately after the onset and after massive myoglobinuria had been present for about 48 hours. The first ECG (Fig. 2, p. 53) was normal apart from tachycardia (130 beats/min.). The second ECG (Fig. 3, p. 54) showed considerably higher and more peaked T waves, although there was still tachycardia (130 beats/min.). According to Merrill *et al.* (1950) high, peaked T waves are an early sign of hyperpotassaemia. In my case, it is possible that the periods of bradycardia (44 beats/min.) which alternated with those of tachycardia (*cf.* p. 47) were a manifestation of transient hyperpotassaemia. Cardiac arrhythmia with bradycardia is, in fact, one of the features of potassium poisoning. Since Case 2 consistently had unimpaired renal function with a large output of urine, it can be presumed that the serum potassium rapidly regained the normal level.

Glucose, Insulin and Adrenalin Tolerance

The results of tolerance tests with oral administration of glucose in these three cases indicated some disturbance in carbohydrate metabolism (Figs. 4—6). In Cases 1 and 2, the curves recorded in 1945 and 1946 were paradoxical, with a high fasting blood sugar level and a marked fall after the intake of glucose. The two glucose tolerance tests made in each of the three cases in May 1954 showed curves of the diabetic type in Cases 1 and 3. No glycosuria was present in either case.

In Case 2, a normal curve was recorded in May 1954. The illness is, however, of relatively short duration in this patient; it is therefore conceivable that a diabetic type of reaction to glucose tolerance tests may gradually develop. It is at present impossible to give any definite explanation of these findings. A noteworthy fact is that both the patients' mother and a maternal uncle have diabetes.

Insulin tolerance tests (Figs. 4—6) showed no conspicuous fall in the blood sugar level in Cases 1 and 3, both of whom had a diabetic type of glucose tolerance curve. In Case 2, on the other hand — in which the glucose tolerance curve was normal — the blood sugar level fell by 50 per cent after the administration of insulin.

In both cases in which an adrenalin tolerance test was made, the blood sugar curve was normal (Figs. 4 and 5), a fact which indicates a normal liver glycogen content.

Creatine and Creatinine Metabolism

Before discussing the creatine and creatinine metabolism in the familial form of myoglobinuria, it is necessary to give a brief account of the metabolism of these substances in man.

Determination of the creatine content of the urine was introduced into clinical practice by Folin (1904), who based his method on Jaffe's discovery in 1886 of the colour reaction of creatinine to picric

acid. During the first decades of the present century, numerous works on the metabolism of creatine and creatinine were published; a survey of them was given by Hunter (1928).

Creatine is not a normal component of the urine other than in small quantities, whereas creatinine is a normal component. In pathologic conditions, creatine may be present, and is then either of exogenous or of endogenous origin. According to Tierney & Peters (1943), creatine is excreted in the urine only when the serum concentration exceeds 0.58 mg/100 ml.

As far as we are aware, the conversion of creatine into creatinine can take place only in the muscles; consequently, the urinary output of creatinine is regarded as a certain criterion of muscular function. The 24-hour output is considerably greater in muscular men than in those with less well developed muscles and in women. Milhorat & Wolff (1937) have given 1.2 to 1.8 g as the normal value for the 24-hour urinary output of creatinine. Considerably higher figures can be recorded in muscular men.

The 24-hour output of creatinine has been calculated in milligrammes per kilogramme of body weight, this figure being denoted as the creatinine coefficient. Myers (1932) gave 18 to 30 as the normal value for the creatinine coefficient in adults, and Milhorat (1953) stated 23 to be the mean figure for adult men.

If the renal factor is disregarded, creatinuria can arise in two essentially different ways. Creatine may either be released from the muscles, or the muscles may be unable to deal with the creatine synthesized by the liver or with that of exogenous origin.

The majority of authors hold the view that adult men do not excrete any creatine in the urine when they are fed on a creatine-free diet. Others have expressed divergent opinions. Light & Warren (1934), Taylor & Chew (1936), Wang (1939) and Wilder & Morgulis (1953) stated that small quantities of creatine are normally present in the urine of adult men. Djen & Platt (1934), Hobson (1939) and Albanese & Wangerin (1944) found considerable quantities in such subjects, but neither the diet nor the physical activity were taken into account.

Creatinuria is physiological in children (*e.g.* Harding & Gaebler 1922, Marples & Levine 1936, Clark *et al.* 1951) and during the puerperium (*e.g.* Shaffer 1908, Zierler *et al.* 1949).

The close relationship of creatinuria to carbohydrate metabolism has been known for many years. Cathcart (1909) was the first to establish that starvation in man resulted in creatinuria, which disappeared after the administration of carbohydrate, but not after that of fats or protein. The same findings were made by Mendel & Rose (1911) in the rabbit. Palladin (1925) also showed that a diet deficient in carbohydrate produced creatinuria in the rat and the guinea-pig.

Brentano (1930, 1932) showed in a series of experiments that the urinary output of creatine increased concurrently with a decrease in the glycogen content of the muscles, and that creatinuria ceased with a rise in the muscle glycogen. He found that the glycogen content of the liver had no effect on the excretion of creatine.

Creatinuria may be present in diabetes. Bürger & Machwitz (1917) found that it invariably occurred in diabetics with permanent acidosis, whereas the creatine metabolism was normal in mild diabetes without the presence of acetone bodies. Frercks (1952) stated that in so-called labile diabetes, creatinuria is an early symptom of some complication or fluctuation, and that it appears before a rise in the blood sugar and glycosuria.

Creatinuria may also be a feature of some endocrine disorders, *e.g.* male hypogonadism and ovarian deficiency (Remen 1932, Mühlbock & Kaufmann 1932, Schittenhelm & Bühler 1934, Comsa 1947). This also applies to thyrotoxicosis (Schaffer 1908, Richardson 1934, Richardson & Shorr 1935, Thorn 1936, Sohval *et al.* 1938, Tierney & Peters 1943, Griffiths 1951). Palmer *et al.* (1929) showed that this creatinuria ceased after iodine therapy. In thyrotoxicosis, there is generally a rise in the serum creatine.

Schrire (1937) found that acidophil tumours of the pituitary are associated with an increased urinary excretion of creatine; this was confirmed by Cumings (1944, 1950).

The administration of methyl testosterone may give rise to creatinuria (Wilkins *et al.* 1941, Hoagland *et al.* 1945, Segaloff *et al.* 1953).

Considerable interest has been focused on creatinuria in muscular dystrophy (Levene & Kristeller 1909, Shank *et al.* 1944, Roche *et al.* 1952, Cumings 1953, Milhorat *et al.* 1937, Milhorat 1953). In muscular dystrophy, there is usually not only pathologic creatinuria, but also a considerable decrease in creatinine excretion, often with a creatinine coefficient below 10. Low retention values are found in creatine tolerance tests. In advanced cases, the excretion of creatine is greater than the urinary output of creatinine. In such cases, the fall in the creatinine content of the urine is parallel to the decrease in muscular function. Creatinuria may also be found in paresis and muscular atrophy of other origin, *e.g.* poliomyelitis (Bröchner-Mortensen 1949, Pollock *et al.* 1954).

Zierler *et al.* attempted to determine the causes of the various conditions of creatinuria from the renal viewpoint. They found that in long-term desoxycorticosterone acetate therapy, in Cushing's disease and during the puerperium, creatinuria was due to a decreased rate of tubular resorption. An increased tubular load of creatine was stated to be the cause of creatinuria in thyrotoxicosis and in methyl testosterone therapy, when the serum creatine level is also high.

A study of the creatine metabolism in the familial form of myoglobinuria is important for two reasons. (1) There is presumably a disturbance in carbohydrate metabolism, and this process is known to be closely related to the metabolism of creatine. (2) Pathologic creatine metabolism is known to be a feature of diseases of the muscles, particularly of muscular dystrophy. Of the few cases of non-traumatic myoglobinuria reported, no less than six were associated with muscular dystrophy.

Determinations of the creatine and creatinine excretion are found in only a few of the earlier reports on myoglobinuria. Moreover, in most of the cases in which such determinations were made, muscular dystrophy was present and the results are therefore difficult to evaluate. Louw & Nielsen's patient, a 10-year-old boy with muscular dystrophy and myoglobinuria, had creatinuria during an attack but not otherwise. In the case described by Kreutzer *et al.* — also combined with muscular dystrophy — the 24-hour urinary output of creatine was 250 mg during the asymptomatic interval and 1,370 mg during the attack. In Acheson & McAlpine's case — a 30-year-old man with muscular dystrophy and myoglobinuria — the excretion of creatine was 610 mg/24 hrs during the asymptomatic interval, the corresponding figure during an attack being 980 mg. Spaet *et al.* had a 23-year-old male patient with paroxysmal myoglobinuria without muscular dystrophy. No creatinuria was present during the attacks or at other times. This is, in fact, the only case in the literature of myoglobinuria without muscular dystrophy in which the creatine metabolism was investigated. Obviously, it is remarkable that no creatinuria occurred when myoglobinuria was present.

A study of the creatine excretion in my cases of the familial form of myoglobinuria showed the presence of large quantities of creatine in the urine during the attacks (Table 4, p. 56). The highest value recorded was 1,644 mg/24 hours. In between the attacks, small quantities of creatine were occasionally found in the urine. When the patients were placed on a low-carbohydrate diet, all three exhibited marked creatinuria. Although determinations were made only on the night urine during the last 12 hours on this diet (experiment 2, p. 52), none of them excreted less than 273 mg (Table 4). Consequently, the 24-hour output of creatine must have been considerably more. According to Powis & Raper (1916) and Denis (1917), practically all the creatine is excreted during the day, whereas the night urine is almost creatine-free. Denis based his statement on a study of various diseases with spontaneous creatinuria.

It is difficult to determine whether the creatinuria in my cases was due to the actual carbohydrate deficiency of the diet, or to the creatine contained in it. According to Thomsen (1938), creatine taken by mouth is excreted during the subsequent 4 to 5 hours. If this is correct, the creatine content of the food would scarcely have been of any decisive importance as a cause of the creatinuria in my cases, since only the night urine was analyzed.

In tolerance tests with the oral administration of 1 g of creatine, all three patients excreted large quantities of creatine in the urine (Table 5, p. 60). Consequently, little of the creatine ingested was retained. Milhorat stated that adult men retained prac-

tically all the creatine ingested; in his tests, he gave 1.32 g by mouth. With an oral dose of 1 g, Pollock *et al.* found 85 per cent retention to be the lowest normal value. In my control series (Table 6, p. 60), the values were comparable with those regarded by Milhorat and by Pollock *et al.* as normal.

Thus, in my cases, tolerance tests showed high values for the urinary output of creatine, on a level with those in severe muscular dystrophy. There is, however, an essential difference from the conditions in the latter disease. All my patients had extremely high values for the urinary excretion of creatinine and, as a result, high creatinine coefficients. A patient with muscular dystrophy and a creatine excretion of the order of magnitude found in my three patients should have an appreciably lower urinary output of creatinine, and a lower creatinine coefficient (Milhorat, Milhorat *et al.*).

It may therefore be inferred from these investigations that a disturbance in creatine metabolism exists, and that it differs essentially from that in muscular dystrophy.

In Cases 1 and 3, curves of the diabetic type were recorded in glucose tolerance tests. According to Bürger & Machwitz, there is, however, normal creatine metabolism in mild diabetes without ketonuria. Although Case 2 had a normal curve for glucose tolerance, a high urinary output of creatine was found in creatine tolerance tests.

Liver Function and Liver Biopsy

Before discussing the results in my cases, mention may be made of some coincident diseases of the liver and muscles reported in the literature.

Several examples are found in veterinary medicine. In a form of toxic liver dystrophy (hepatosis diabetica) in swine, Obel (1953) found waxy degeneration of the skeletal muscles in 60 per cent of the cases. In enzootic myoglobinuria in the horse, fatty degeneration of the liver may be found (Carlström 1933), as well as liver necrosis (Irwin & Pulsford 1947).

Concurrent lesions of the liver and muscles also occur in man. In Weil's disease, of which one of the features is widespread degenerative changes in the liver, the muscles exhibit degenerative lesions on microscopic examination. Adams *et al.* (1953) described several cases of this disease in which Zenker's degeneration was present in the muscles. Hjärre (1952) stated that there is probably a close pathogenetic relationship between the waxy degeneration of the muscles and the central lobular necrosis of the liver.

Although liver damage has been mentioned in several cases of myoglobinuria in man, its possible relationship to the muscular lesions has not been discussed. For example, Hittmair stated that his patient had moderate hepatomegaly, but he did not give any further details. Hörman reported on a patient who died of an attack of myoglobinuria; the liver was palpable four fingerbreadths below the costal margin. The icterus index (Meulengracht) was 19. At autopsy, the liver exhibited marked, large-globular fatty degeneration. The patient described by Spaet *et al.* had a serum bilirubin

value of 2.2 mg/100 cc during an asymptomatic interval, and the cephalin flocculation was 3+.

In my Case 4 (p. 86) there is possibly incipient cirrhosis of the liver, and in Case 5 (p. 90) fatty degeneration of the liver.

In the investigation of the liver function in the three cases now under discussion, the striking features are the raised serum bilirubin level and the pathologic increase in the urinary urobilin. Such values were recorded intermittently between the attacks of myoglobinuria.

At first sight, these pathologic concentrations would appear to be a result of the myoglobinaemia, and thus to be analogous to the increased concentrations of bilirubin and urobilin found in haemolysis.

However, none of the investigations made have shown any rise in the serum bilirubin during the actual attacks of myoglobinuria (*e. g.* Wissler, Jasiński & Brütsch). In paralytic myoglobinuria in the horse, Carlström found a rise in the serum bilirubin only in severe cases, and it did not appear until the second or third day. Since at this stage complications have had time to develop, this observation is difficult to interpret. (It may be mentioned as a comparison that, in intravascular haemolysis in the horse, Bendixen & Carlström found an increase in the serum bilirubin already after 2 to 4 hours.) It seems feasible to attribute the absence of any rise in the serum bilirubin during the attacks to the fact that myoglobin is excreted through the kidneys 25 times more rapidly than haemoglobin. Consequently, it is not taken up by the reticulo-endothelium to the same extent as is haemoglobin.

In 1946, an attack of myoglobinuria was provoked in Case 2 by means of a low-carbohydrate diet (experiment 1, p. 50). Since a rise in the serum bilirubin was noted 26 hours before the appearance of myoglobinuria, it cannot reasonably have been a result of myoglobinaemia. A further indication is given by the fact that a normal value for the serum bilirubin was recorded three days after the onset of myoglobinuria; during this time there had been a massive urinary excretion of myoglobin. Large quantities of sugar were administered during these three days. If myoglobinaemia were responsible for the rise in serum bilirubin, it is obvious that a high value would have been found after myoglobinuria had been present for three days. In experiment 2 (p. 52) an increase in the serum bilirubin was noted in two of the cases after 48 hours on a low-carbohydrate diet (Table 8, p. 61). A fall to below the initial level took place in the two cases in which extra sugar was given at the end of the experiment.

Consequently, the rise in serum bilirubin must presumably be regarded as a parallel phenomenon to the myoglobinaemia, but not as a direct result of it.

It may be recalled that starvation is associated with a rise in the serum bilirubin and an increased urinary excretion of urobilin. Normally, the serum bilirubin is highest in the morning and falls after meals. Bröchner-Mortensen (1935) and Fellinger & Pleger (1935) found a distinct fall in the serum bilirubin four hours after a meal; the fall was more marked after the intake of fats and carbohydrate than after that of

protein. Meyer & Knüpffer (1922) found an increase of 20 to 200 per cent in the blood content of bilirubin in healthy subjects after 24 hours' starvation. Huhtala (1937) reported a rise in the serum bilirubin ranging from 100 to 200 per cent after 22 to 36 hours' starvation. If the subjects performed muscular work during this time, the rise was still greater; values of up to 600 per cent of the normal values were then recorded. The cause of this rise in the serum bilirubin in starvation is not yet fully elucidated.

The urinary excretion of urobilin in starvation was described for the first time by Naunyn (1869). Since then, similar observations have been reported by Adler & Sachs (1923), Fischler & Ottensooser (1925) and Heilmeyer & Oetzel (1931), among others. Bang (1929) showed that a low-carbohydrate diet resulted in an increased urinary output of urobilin. The essential factor was found to be the carbohydrate deficiency and not the increased meat, fat or egg content of the diet. When carbohydrates were once more given, the urobilinuria ceased. Bang expressed the view that a transient impairment of liver function developed, owing to glycogen deficiency. His results could not be verified in every respect by Åkerrén (1934).

In my three cases, the bilirubin tolerance test showed definitely raised retention values (Table 11, p. 63). The upper borderline for normal retention is given by Eilbott as 10 per cent and by Strasser (1937) as 20 per cent.

Bröchner-Mortensen investigated the bilirubin tolerance method and found it to be less sensitive than the bromsulphalein and the galactose tolerance test as a gauge of liver damage. In a series of 25 normal subjects, he found no retention in 10 cases, up to 10 per cent in 11 and from 10 to 15 per cent in 4 cases.

The reliability of the method was also analyzed by With (1943). In a series of 24 normal subjects, the highest retention value was 25 per cent. He nevertheless found a poor correlation between the degree of retention and the clinical features in diseases of the liver, particularly in acute hepatitis.

In the form of jaundice described by Gilbert (1901) as *cholémie simple familiale*, denoted by Meulengracht (1939) as *icterus intermittens juvenilis*, and by Alwall (1945) and Alwall *et al.* (1946) as hereditary, non-haemolytic hyperbilirubinaemia, the bilirubin tolerance test shows extremely high retention values (Dameshek & Singer 1941, Alwall 1945, Welin 1945, Ljung 1948).

Histologic examination of a biopsy specimen from the liver in one of my cases showed marked fatty degeneration. This may be present in some residual states following hepatitis (Hult 1950). There are, however, no grounds for interpreting the hyperbilirubinaemia in these three cases as a residual state following a previous attack of hepatitis.

Thus, the studies of the liver gave the following positive data: a pathologic increase in the urinary excretion of urobilin, a raised serum bilirubin level and pathologic bilirubin tolerance in all three cases, and fatty degeneration of the liver in one case. These findings must presumably be regarded as an indication of some form of liver damage.

Thyroid Function

It has long been known that a relationship exists between thyroid dysfunction and certain diseases of the muscles. Thyrotoxicosis combined with muscular disease was described by Bathurst already in 1895 and by Askanazy in 1898.

Brain & Turnbull (1938) divided the thyrogenic muscular diseases into five groups:

1. Acute thyrotoxic myopathy
2. Chronic thyrotoxic myopathy
3. Thyrotoxic periodic paralysis
4. Myasthenia gravis and thyrotoxicosis
5. Exophthalmic ophthalmoplegia

1. **Acute thyrotoxic myopathy** is an often virulent form with an acute course and is usually associated with thyrotoxic crises and encephalopathy. Waldenström (1945) described 10 such cases; the 7 most recent ones recovered after treatment with large doses of iodine and thyroidectomy.

2. **Chronic thyrotoxic myopathy** most frequently affects men, although thyrotoxicosis in general is most common in women (Morgan & Williams 1940, McEachern & Ross 1942, Thorn & Eder 1946, Quinn & Worcester 1951, Zierler 1951, Sanderson & Adey 1952). The syndrome is characterized by progressive, symmetric muscular weakness and atrophy, the shoulder and pelvic muscles being most often involved. The symptoms of thyrotoxicosis are often minimal and the disease is therefore liable to be misinterpreted as progressive muscular dystrophy. Dramatic improvement may result from treatment of the hyperthyrosis.

3. **Thyrotoxic periodic paralysis.** Shinosaki (1925) gave an account of 25 cases. Goitre was present in 62 per cent; in 29 per cent it was toxic and in 33 per cent non-toxic. Shinosaki was the first to succeed in provoking attacks by means of thyroid extract. Later workers have not found the same high incidence of thyrotoxicosis in familial periodic paralysis as did Shinosaki. According to Millikan & Haines (1953), periodic paralysis sometimes exists as a latent anomaly, which becomes manifest through thyrotoxicosis. The symptoms may disappear after treatment of the hyperthyrosis.

4. **Myasthenia gravis** may occur in combination with thyrotoxicosis (Levy *et al.* 1951).

5. **Exophthalmic ophthalmoplegia.** Generalized muscular disease is seldom present concurrently.

In my Case 1, attacks of myoglobinuria occurred before thyrotoxicosis developed, but they became worse after this event. Moreover, the patient stated that they became reduced in both frequency and intensity by about 50 per cent after thyroidectomy. Although Case 2 had a goitre, there was no thyrotoxicosis; no improvement with respect to the myoglobinuria has taken place after thyroidectomy. It is probable that in the familial form of myoglobinuria, an exacerbation occurs in the presence of thyrotoxicosis, in similarity to the relationship between periodic paralysis and thyrotoxicosis described by Millikan & Haines.

Adrenocortical Function

Acheson & McAlpine are the only authors to report a determination of the urinary excretion of 17-ketosteroids in myoglobinuria. They found a high output in their patient, who also had muscular dystrophy.

In my three cases, normal values were found for the 24-hour total output of 17-ketosteroids and corticosteroids (Table 13, p. 65). In Case 3, the microchromatograms showed a rise in the fraction in which dehydroepiandrosterone is present, the mean value being 26.8 per cent of the total output of 17-ketosteroids. Plantin & Birke have given 5.8 to 8.5 per cent as the normal value for the excretion of dehydroepiandrosterone. Birke (1954) found an increased excretion of this fraction under various conditions of stress.

The results of the determinations of the urinary output of 17-ketosteroids and corticosteroids give no grounds for supposing that the adrenal cortex is implicated in the pathogenesis of the familial form of myoglobinuria. The rise in the dehydro-epiandrosterone fraction found in one of the cases might be an indication of some condition of stress. Further observation is, however, necessary before any definite statement can be made.

Neurological Examinations

No less than six of the cases of paroxysmal myoglobinuria reported in the literature were combined with muscular dystrophy. Consequently, it is of prime importance in a case of myoglobinuria to determine whether muscular dystrophy is present.

During asymptomatic intervals, neurological examinations showed entirely normal conditions in every case, with no clinical signs of muscular dystrophy. All three patients are well-trained sportsmen, and they have no muscular atrophy, hypertrophy or paresis. Electromyographic tracings disclosed nothing pathologic.

There is definitely no paresis during the mild and the moderately severe attacks. The electromyographic tracing made in Case 3 during a mild attack showed a normal response. This was despite the fact that the recording was made from the gastrocnemius muscle, which was one of the groups of muscles then affected. Moreover, a determination of the myoglobin content of a biopsy specimen taken from this muscle two days after the same attack showed it to be low (*cf.* p. 67), indicating a release of myoglobin from the muscles.

During the infrequent extremely severe attacks, it is difficult to decide whether or not any true paresis is present. An attack of myoglobinuria is associated with excruciating pain and tenderness in the muscles, making the patients incapable of movement. This difficulty in moving the extremities owing to pain and tenderness is liable to be interpreted as true paresis. On the other hand, any actual paresis can be overlooked at this stage.

Muscular weakness is one of the features of potassium poisoning. In extremely severe attacks of myoglobinuria, the serum potassium may be raised (*cf.* Case 5, p. 90). Buchanan & Steiner's patient died of respiratory paralysis, and it is not improbable that hyperpotassaemia was the actual cause of death. It cannot be ruled out that hyperpotassaemia with paresis may occur during the severe attacks in the familial form of myoglobinuria as well.

Mental changes during attacks of myoglobinuria have been reported by Paul and by Hittmair. Paul wrote: "Im Vordergrund des Krankheitsbildes steht aber die grosse Hinfälligkeit der Pat. und ihre fast vollkommene geistige Apathie." Hittmair stated that his patient was "leicht benommen und phantasierte etwas". In this case, the mental anomalies recurred in every attack: "Schlaflosigkeit, Unruhe, Benommenheit und andere leichte zerebrale Reizerscheinungen fehlen anscheinend nie."

My patients exhibit some mental anomalies during the attacks. They are often strikingly lethargic and apathetic. This applies in particular to Case 2 during a severe

attack (*cf.* p. 47). He then had visual hallucinations. A definitely pathologic electroencephalogram was recorded in this patient during an asymptomatic interval. The EEGs of the two other patients, also recorded in between attacks, were normal.

During the asymptomatic intervals, I have seen no signs of any abnormal mental reactions in any of the patients.

Histologic and Chemical Examination of Biopsy Specimens

Conspicuous muscle changes have been found at autopsy in patients who died during an attack of myoglobinuria. In Paul's case there was waxy degeneration, and in Günther's there was myositis with degenerative, inflammatory and necrotic lesions. Bywaters & Dible's case exhibited degenerative changes with necrosis, Buchanan & Steiner's waxy degeneration, and Hörman's degenerative lesions. On the other hand, Spaet *et al.* were unable to find any definitely pathologic changes in examination of a biopsy specimen of muscle, although their patient had had about 50 attacks. In veterinary medicine, there is no known case of myoglobinuria without coincident waxy degeneration of the muscles.

Against this background, it is surprising that histologic examination showed no pathologic changes in the muscle in my cases. Determination of the myoglobin content of the biopsy specimen of muscle in Case 3 showed it to be low (*cf.* p. 67). Consequently, this affords evidence of a probable loss of myoglobin from the specimen examined histologically.

This fact lends support to the supposition that myoglobin can be released without total breakdown of the muscle cells. It is therefore probable that the release of myoglobin in these familial cases of myoglobinuria is associated with muscle damage of such a nature that it cannot be demonstrated with the usual histologic technique.

Prognosis

The patients have now been under my observation for 10 years. As far as the individual attacks of myoglobinuria are concerned, the prognosis *quoad vitam* must be regarded as good. There are, however, always two risks to be envisaged during an attack: (1) renal failure with oliguria or anuria, and (2) hyperpotassaemia. It is true that no severe renal damage has hitherto been found in these patients, but experience in other forms of myoglobinuria (*cf.* Cases 4 and 5, pp. 86 and 90) gives reason to presume that such damage can also occur in the familial form. Hyperpotassaemia of any clinical importance would probably arise only during an extremely severe attack, and would presumably be life-threatening only if renal failure with oliguria or anuria were present concurrently (*cf.* Case 5, p. 90).

With respect to the metabolic disturbance which exists in all three cases, the prognosis is more uncertain. Liver damage is already present. (It may be mentioned that in my Case 4 — not belonging to the familial form of myoglobinuria — there is probably incipient cirrhosis of the liver.) Nor can it be ruled out that all three patients have latent diabetes, which will gradually become manifest.

Therapy

The aetiology of the familial form of myoglobinuria is not yet fully elucidated; consequently, no causal therapy exists. The attacks occur only on overexertion and when the carbohydrate intake is inadequate. The patients should therefore have an occupation that does not make excessive demands on their muscular force, and their daily diet should have a high content of easily digestible carbohydrate.

In acute infections, the patients should remain in bed and be given extra sugar. When an incipient attack is suspected, large quantities of sodium bicarbonate and fluids should be administered without delay. Even if the precipitation of myoglobin crystals in the renal tubules is not the only explanation of the renal damage in these cases, the sodium bicarbonate may contribute to keeping the myoglobin in solution (*cf.* p. 53).

Thus, the three cardinal points of therapy are: avoidance of overexertion, regular meals with a high-carbohydrate content, and the administration of sodium bicarbonate when an attack is imminent.

Relationship of Familial Paroxysmal Myoglobinuria to Certain Other Diseases

The three diseases that seem most likely to bear some relationship to the familial form of paroxysmal myoglobinuria are muscular dystrophy, familial periodic paralysis and acute porphyria.

1. **Muscular dystrophy.** No less than six of the few patients with paroxysmal myoglobinuria reported in the literature suffered from muscular dystrophy. When two so relatively uncommon diseases are present concurrently, there is naturally reason to suspect the existence of some mutual relationship. Consequently, one of the first questions that arises in a case of paroxysmal myoglobinuria is whether the patient may have muscular dystrophy.

In my three cases, there are no symptoms or signs of muscular dystrophy. Neither paresis, muscular atrophy nor hypertrophy is present. The patients are now respectively 29, 30 and 35 years old. In the event of their suffering from this hereditary disease, some manifestations would obviously have appeared by this time. A genetic study disclosed no case of muscular disease among the patients' relatives (*cf.* Chap. VI). Examination of a biopsy specimen from the muscles in two of the cases showed a normal histologic appearance. Moreover, electromyographic recordings revealed nothing pathologic.

The disturbance in creatine metabolism differs distinctly from that found in muscular dystrophy. Thus, my patients have no decreased urinary output of creatinine, the creatinine coefficient being high in every case.

The impairment of carbohydrate metabolism present in my three cases is not generally regarded as a feature of muscular dystrophy. A few reports of endocrine dysfunction as the cause of this disease are, however, found (Janney *et al.* 1918, Bramwell 1925) including specific impairment of carbohydrate metabolism (McCrudden & Sargent 1916, Meldolesi 1939). Meldolesi stated that changes in carbohydrate metabolism

were consistently present in his series of patients with muscular dystrophy. In glucose tolerance tests, he found an increase and a prolongation of the hyperglycaemia. He did not, however, give any numerical results in support of his statements. Tyler & Perkoff (1951) gave accounts of a thorough investigation of a large series of patients with muscular dystrophy, and also analyzed Meldolesi's statements. The carbohydrate metabolism was investigated by means of both oral and intravenous tests of glucose tolerance. Despite comprehensive investigations, none of Meldolesi's results could be verified. The authors summarized their findings as follows. "Other studies, including morphologic blood studies and serum chemical determinations and routine urine examinations, did not reveal evidence of a significant abnormality in the blood or renal system. Those abnormalities which have been observed can be accounted for by the decrease in muscle mass present in progressive muscular dystrophy."

In the form of myoglobinuria associated with muscular dystrophy, it seems as though myoglobin is released only from those muscles affected by the dystrophic process. In the familial form of myoglobinuria, on the contrary, no particular groups of muscles are susceptible; all the striated muscles may be affected, even if the symptoms appear first in the muscles under stress at the time.

2. **Familial periodic paralysis.** In this disease, true paresis is present, together with hypopotassaemia. In familial paroxysmal myoglobinuria, there is probably no paresis. The limitation of movement during the attacks can be ascribed to the pain and tenderness in the muscles. Only during the severe attacks is there a possibility of hyperpotassaemia of such an order of magnitude that paresis might arise.

An attack of myoglobinuria can be provoked in my patients by means of a low-carbohydrate diet. In familial periodic paralysis, attacks can, on the contrary, be precipitated by means of a high-carbohydrate diet; this has been demonstrated by Shinosaki (1925), Talbott (1941), Ziegler (1949), Ziegler & McQuarrie (1952) and McQuarrie & Ziegler (1952), among others. Moreover, attacks at close intervals cease if the patient is placed on a low-carbohydrate diet or is deprived of food for a few days. Thus, a deficiency of carbohydrate — which produces attacks in familial paroxysmal myoglobinuria — inhibits a current attack and prevents the occurrence of further attacks in familial periodic paralysis. In this respect, the conditions seem to be diametrically opposed in the two diseases.

3. **Acute porphyria.** Certain similarities exist between this disease and familial paroxysmal myoglobinuria. In both cases the attacks are associated with difficulty in urinating and a rise in blood pressure. Tachycardia, leukocytosis and mental anomalies may also occur in both conditions. The cardinal symptoms of acute porphyria — abdominal pain, vomiting and constipation (Waldenström 1937) — are, however, lacking in my cases. In some cases of porphyria, there may be marked muscular symptoms, and depigmentation of the muscles has then sometimes been found at autopsy. Such cases have been described by Waldenström (1934), Vannotti (1935), de Langen (1943) and Beltoni (1947), among others. Vannotti introduced the term myoporphyria for this condition. He stated that, in such cases, the porphyrins are formed by breaking down of myoglobin,

and that the disease can be regarded as analogous to myoglobinuria. It would represent the physiological means by which the body rids itself of the myoglobin released from the muscles. Waldenström (1939) has, however, stressed that this condition does not differ from ordinary acute porphyria, and that the term myoporphyrria lacks any factual basis. It is considered that porphyrins are formed only during haemoglobin synthesis and not during dissolution (Rimington 1952).

The presence of porphyrins in the urine has not been observed in any case of paroxysmal myoglobinuria. In my three cases, no porphyrins were found in the urine during the attacks.

7. *Summary*

An account is given of the clinical picture in three cases of familial paroxysmal myoglobinuria. The characteristic features are provocation of the attacks by muscular exertion and by a low-carbohydrate diet, pathologic glucose tolerance curves and pathologic creatine metabolism. The implication of these findings is discussed, as well as the possible relationship of the disease to certain other diseases.

A GENETIC STUDY OF
THE CASES OF FAMILIAL PAROXYSMAL
MYOGLOBINURIA

1. *Introduction*

Since the three patients (Cases 1—3) with familial paroxysmal myoglobinuria are brothers, it seemed highly probable that a genetic factor played some role in the aetiology of the disease. In order to determine whether this was so, I made a genetic study covering five generations of the family of these patients (denoted in the following as the probands). Its object was to ascertain the possible occurrence of cases of any of the following groups of diseases:

1. Myoglobinuria
2. Muscular dystrophy
3. Other diseases possibly related to myoglobinuria

2. *Methods*

Registration of the Relatives

The four pairs of parents of the probands' grandparents were taken as the basis for the investigation. These pairs of parents were registered as nos. 1—4. The individuals in the second generation were given two-digit numbers, the first digit being the number of the ancestor, and the second digit the parity number in the sibship of the individual in question. Similarly, the individuals in the third, fourth and fifth generations were given three, four and five-digit numbers, respectively. Since none of the persons concerned had more than nine children, this method of registration could be used consistently.

Altogether, 257 living and 123 deceased relatives of the probands were registered. The majority of these persons live — or had lived — in the province of Ångermanland in northern Sweden; only a few lived in or near Stockholm or elsewhere.

Investigation of the Relatives

As I have already stated, the object of the genetic study was to trace any cases of myoglobinuria, muscular dystrophy or other diseases possibly related to myoglobinuria in the probands' family. With respect to myoglobinuria, the main feature of

the investigation was a detailed case history of each individual. When special reasons existed — *e.g.* close relationship to the probands or a statement in the history giving grounds to suspect myoglobinuria — a creatine tolerance test was made, using the method described in Chapter IV.

My search for cases of muscular dystrophy was based on the case history and on a complete neurological examination, in view of the four main groups of muscular dystrophy:

- I. Duchenne-Griesinger's infantile pseudohypertrophic atrophy of the hips and buttocks
- II. Leyden-Möbius's infantile atrophic form with the same localization
- III. Erb's juvenile atrophy of the shoulders
- IV. Landouzy-Dejerine's infantile atrophy of the muscles of the face and the scapulo-humeral region.

Diabetes, familial periodic paralysis and porphyria were the other diseases with a possible relationship to myoglobinuria on which I focused particular interest when taking the histories.

Of the 257 living relatives registered, I met and investigated 153 according to the aforementioned principles. They included all the closest relatives of the probands, *e.g.* parents, siblings, siblings' children, and cousins. I was unable to make personal contact with the remaining 104 persons, but it was generally possible to obtain satisfactory data about them from other members of the family. As far as the deceased persons were concerned, I obtained the cause of death from the parish registers in those cases in which it was given. In addition, some information regarding their history was supplied by close relatives.

3. Results

The genetic study disclosed no definite cases of myoglobinuria. Two cousins of the probands' mother had muscular complaints similar to those in the familial form of myoglobinuria. A brief account of these cases is given in the following.

No. 442. A 53-year-old man. As long as he could remember, exertion had brought on pain in the muscles, chiefly in those of the calves and thighs. The symptoms appeared only on exertion, but they were more liable to occur if he neglected to eat properly. He had never noticed any discoloration of his urine.

Physical examination disclosed nothing noteworthy. Urine: tests for protein and reducing substance negative. In two creatine tolerance tests, the 24-hour excretion of creatine was 220 and 170 mg, respectively.

No. 463. A 43-year-old man. He served his first term of military service as fit for active service. Since he was about 23 years old, exertion had produced aching and tenderness in the muscles. The muscles of his arms and calves were sometimes so tender that he could scarcely bear to touch them. He had not noticed whether the symptoms were accentuated by neglect of food, nor had he noticed the colour of his urine.

Physical examination showed nothing noteworthy. Urine: tests for protein and reducing substance negative. In a creatine tolerance test, he excreted no creatine.

Investigation of the parents and siblings of the probands gave the following results.

No. 1511. Father, b. May 8, 1892. No subjective discomforts. Physical examination showed nothing noteworthy. Urine: tests for protein and reducing substance negative. Creatine tolerance test: no excretion of creatine.

No. 434. Mother, b. March 14, 1898. She has had diabetes since about the age of 40 and has taken insulin for the past year. Physical examination: nothing noteworthy. Creatine tolerance test: no excretion of creatine.

No. 1512. Sister, b. July 27, 1921. Physical examination: nothing noteworthy; no signs of thyrotoxicosis. A number of diffuse muscular complaints, chiefly in the form of aching and fatigue of the spinal muscles. Urine: tests for protein and reducing substance negative. In two creatine tolerance tests, the 24-hour excretion of creatine was 600 and 800 mg, respectively.

No. 1513. Brother, b. Aug. 30, 1922. No subjective complaints. Physical examination showed nothing noteworthy. Urine: tests for protein and reducing substance negative. Creatine tolerance test: no excretion of creatine.

No. 1516. Brother, b. June 6, 1929. No subjective complaints. Physical examination showed nothing noteworthy. Urine: tests for protein and reducing substance negative. Creatine tolerance test: no excretion of creatine.

Despite a thorough search and close questioning with respect to possible symptoms, no case of muscular dystrophy was found among the probands' relatives.

As far as other diseases are concerned, it may be stressed that the probands' mother and one of her brothers have diabetes. With these exceptions, no other disease that could conceivably bear any relationship to the familial form of myoglobinuria could be traced, either on direct contact with the relatives, or on a search of the parish registers for the cause of death in the deceased members of the family.

4. Discussion

No additional case of familial paroxysmal myoglobinuria was disclosed by the genetic study. The disease may, however, be present in a mild form and then be asymptomatic. The probands were all active sportsmen, and their attacks were precipitated mainly by muscular exertion in this connexion. It is not unlikely that the disease can remain undiagnosed in persons who do not exert their muscles unduly.

Moreover, myoglobinuria need not necessarily be present in every case. The probands, for example, sometimes had typical muscular manifestations without any discoloration of the urine. It is conceivable that there may be cases in which the symptom complex is incomplete. Nos. 442 and 463 had muscle complaints similar to those of the probands; it is possible that they actually suffer from familial paroxysmal myoglobinuria, although the symptom complex is not fully developed. As long as our only possibility of diagnosing the disease is the demonstration of myoglobin in the urine, this question must remain open.

An interesting feature is that the probands' mother as well as one of their maternal uncles have diabetes.

5. Summary

An account is given of the methods used in a genetic study of the probands' relatives and of the results obtained. It was not possible to trace any definite case of myoglobinuria in the family, nor any case of muscular dystrophy.

THREE CASES OF NON-FAMILIAL MYOGLOBINURIA

1. *Introduction*

In addition to the three cases of familial paroxysmal myoglobinuria discussed in Chapters V and VI, I have had the opportunity — either personally or by means of the relevant data supplied by colleagues — of studying a further three cases of myoglobinuria. These cases provide examples of different forms of the disease which, from the clinical viewpoint, differ essentially in certain respects from the familial form. For this reason, and in order to illustrate some other matters of interest in myoglobinuria, an account of these cases is given in the following.

2. *Case Histories*

Case 4. A man, b. Aug. 23, 1914. Building joiner.

Heredity. His father was killed in an accident when the patient was a child. His mother, aged 65, is alive and healthy. His only brother was killed in an accident; he has one stepbrother. No family history of nervous or mental diseases or of any complaint resembling the patient's.

Social-hygienic conditions. Married, three children. Did his military service as fully fit for active service. Drinks and smokes in moderation. Venereal diseases denied.

Diet. Has lived on a normal diet, with plenty of milk, eggs and vegetables.

Earlier illnesses. Treated at the surgical clinic of Västerås Hospital from May 8—13, 1939 for thrombophlebitis of the right lower leg, and from June 12—23 for haematoma of the right lower leg. 1944, fracture of the left lower leg; admitted to Karolinska Sjukhuset.

Present illness. Six years in succession (1945—1950), invariably at Christmas, there had been an attack of muscular pain and stiffness; the symptoms usually started with a dragging feeling in the calf muscles and spread to the muscles of the thighs, back, nape and arms. The patient also passed thick, dark-brown urine. In between the attacks, he was asymptomatic and was able to do heavy work. He had never noticed that the attacks were brought on by exertion, nor were they more liable to occur if he exerted himself on an empty stomach.

The first attack started in the afternoon of Dec. 23, 1945, with pain and stiffness of the leg and lumbar muscles. He could not stand up and his temperature was 40° C. Poliomyelitis was suspected. He was admitted to hospital on December 24. The Lasègue sign was then + 30° bilaterally. A diagnosis of acute glomerulonephritis and lumbago was made. (For the laboratory data, see Table 14.) He was discharged from hospital on Feb. 1, 1946, but still felt tired and weak and was unable to start work until the middle of March.

He was subsequently in good health and able to work until Christmas 1946, when he once again had an attack of severe muscular pain and tenderness, associated with passage of dark-brown urine. The discoloration of the urine lasted for about a week. The attack was followed by fatigue and muscular weakness, so that he did not start work until the middle of April 1947. This brought on a recurrence of muscular pain and discoloured urine, lasting for only slightly more than 24 hours.

On account of these complaints, he was in the medical department of Västerås Hospital from May 5—17 and June 20—30, 1947. On admission, his urine was pale and clear, but exertion produced a

TABLE 14

	27/12-45	2/1-46	5/1-46	10/1-46	16/1-46	30/1-46
Protein in urine	o	Traces	o	o	o	o
Urinary sediment	o	4-5 R. B. C./ vis. field	5-8 R. B. C./ vis. field	o	o	o
N. P. N. mg/100 ml	180	180	138	80	40	30
S. R. mm/1 hr	27	39	55	43	35	28

TABLE 14. Case 4. Results of some blood tests and urinalyses in 1945-1946.

dragging and stretching sensation in the arms and the back of the thighs. Physical examination showed the following. *Heart*: nothing abnormal. *Blood pressure*: 135/85 mm Hg. *Reflexes*: pupillary, patellar and Achilles reflexes normal. Babinski's sign negative bilaterally. Lasègue's sign: right + 80°, left + 70°.

Blood tests: haemoglobin 88 %. R. B. C. 4,700,000. W. B. C. 5,100. Differential cell count: 67 % neutrophils, 4 % eosinophils, 0 % basophils, 16 % lymphocytes and 13 % monocytes. Non-protein nitrogen: 28 mg/100 ml. S. R. (mm/1 hr): 5/5, 25 mm; 15/5, 24 mm; 20/6, 20 mm.

Urinalyses: tests for protein and reducing substance negative; nothing pathologic in the sediment. Specific gravity: 1.025.

At a check-up in the out-patient department on July 14, the patient was found to be asymptomatic. The S. R. was then 4 mm/1 hr. He was subsequently free from complaints, with the exception of an attack in December 1947 and another in December 1948. On each occasion he was unable to work for three weeks.

On Dec. 24, 1949 he had a fresh attack of pain and a feeling of stiffness in the muscles; on the following day his urine was dark-brown. His temperature rose to 39.3° C but returned to normal the next day. He was admitted to the medical department of Västerås Hospital on December 29. The muscular aches had then started to subside and movement of his arms and legs was no longer painful. His urine had also started to become paler, but was still definitely discoloured on the first day in hospital. Physical examination showed the following. *Heart*: nothing abnormal. *Blood pressure*: 120/80 mm Hg. *Lungs*: nothing abnormal. *Abdomen*: nothing abnormal. *Reflexes*: pupillary, patellar and Achilles reflexes normal. Babinski's sign negative bilaterally. Lasègue's sign negative bilaterally. — During his whole stay in hospital he was afebrile.

Blood tests: haemoglobin 91 %. W. B. C. 5,400. Differential cell count: 71 % neutrophils, 3 % eosinophils, 0 % basophils, 13 % monocytes, 13 % lymphocytes. Total serum protein 7.7 %. Icterus index (Meulengracht) 4. *Urinalyses*: no reducing substance. Bile pigments: slight traces of urobilin. Hammarsten's test negative. Tests for porphyrins and myoglobin (Prof. G. Blix): no uroporphyrin. Benzidine test positive. Spectroscopic examination showed the presence of fairly large quantities of myoglobin. *Renal function*: creatinine clearance 132 ml/min. Concentration to 1,013, dilution to 1,009. *Glucose tolerance test*: fasting blood sugar 119 mg/100 ml; after 15 min. 146 mg; 30 min. 185 mg; 45 min. 201 mg; 60 min. 168 mg; 90 min. 164 mg; and 120 min. 115 mg/100 ml. — For other laboratory data, see Table 15.

On discharge from hospital on Jan. 13, 1950 the patient was greatly improved, but he still felt tired and weak and could not start work until three weeks later.

Since then, he has been in good health, except for an attack of muscular pain associated with the passage of dark-brown urine at Christmas 1950. He was away from work for three weeks, but did not require hospitalization.

On Oct. 4, 1954, he was admitted to Medical Department IV of Södersjukhuset for further investigation. The results were as follows (Case-sheet no. 15687/54). *General condition*: no systemic disturbances. No cyanosis or dyspnoea. No oedema. *Throat and oral cavity*: nothing abnormal. *Thyroid*: no palpable enlargement. *Heart*: sounds pure, rhythm regular. *Blood pressure*: 125/80 mm Hg. *Lungs*:

TABLE 15

	29/12-49	31/12-49	5/1-50	7/1-50	9/1-50
Protein in urine	0.1 %	0.2 %	Traces	0	0
Urinary sediment	0	0	0	0	0
N. P. N. mg/100 ml	43	—	44	—	34
S. R. mm/1 hr	32	—	95	—	62

TABLE 15. Case 4. Results of some blood tests and urinalyses in 1949-1950 (*cf.* p. 87).

nothing abnormal. *Abdomen*: nothing abnormal. *Reflexes*: pupillary, patellar and Achilles reflexes normal. Babinski's sign and Lasègue's sign negative bilaterally. No neck rigidity. No paresis. Muscular tonus normal. No myotonic or myasthenic reactions. No muscular atrophy or hypertrophy.

Blood tests: haemoglobin 88 %. R. B. C. 4,600,000. W. B. C. 3,200. Differential cell count: 53 % segmented neutrophils, 1.5 % stab neutrophils, 3.5 % eosinophils, 35 % lymphocytes, 7 % monocytes. Thrombocytes 140,000. Reticulocytes 0.7 %. S. R. 19 mm/1 hr. Serum electrolytes: sodium 142 mEq./L, potassium 3.6 mEq./L, calcium 10.0 mg/100 ml, phosphorus 2.5 mg/100 ml.

Urine and renal function: tests for albumin and reducing substance negative; nothing pathologic in the sediment. Concentration to 1,027, dilution to 1,004. Non-protein nitrogen 26 mg/100 ml.

Glucose tolerance test: fasting blood sugar 120 mg/100 ml; after 30 min. 196 mg; 60 min. 141 mg; 90 min. 135 mg; 120 min. 133 mg; 150 min. 104 mg/100 ml. *Adrenalin tolerance test*: fasting blood sugar: 125 mg/100 ml; after 15 min. 143 mg; 30 min. 139 mg; 45 min. 135 mg; 60 min. 120 mg; 90 min. 126 mg; 120 min. 130 mg; 150 min. 120 mg/100 ml.

Urinary creatine and creatinine excretion: see Table 16. Urinary output of 17-ketosteroids: 12.5 mg/24 hrs; corticosteroids: 9.9 mg/24 hrs. Microchromatogram normal.

Liver function: thymol turbidity 10.5 units. Serum phosphatase (Bach) 3.2 units/100 ml. Serum cholesterol 203 mg/100 ml. Takata reaction positive: precipitation 0, 0, 3, 3, 2 1/4, 1 3/4, 1, 0. Prothrombin index 88 %. Total serum proteins 8.4 %. Fibrinogen 0.43 %. Electrophoresis on serum protein: albumin + α_1 globulin 49 %, α_2 globulin 6 %, β globulin 12 %, γ globulin 33 %. Serum bilirubin and urinary urobilin: see Table 17. Hippuric acid excretion 5.4 g/4 hrs. Galactose tolerance:

TABLE 16

	Creatine mg/24 hrs	Creatinine mg/24 hrs
Before tol. test	0	1,875
After tol. test, 1 g orally	0	1,395
After 3 days low-carbohydrate diet	0	1,872

TABLE 16. Case 4. 24-hour urinary excretion of creatine and creatinine.

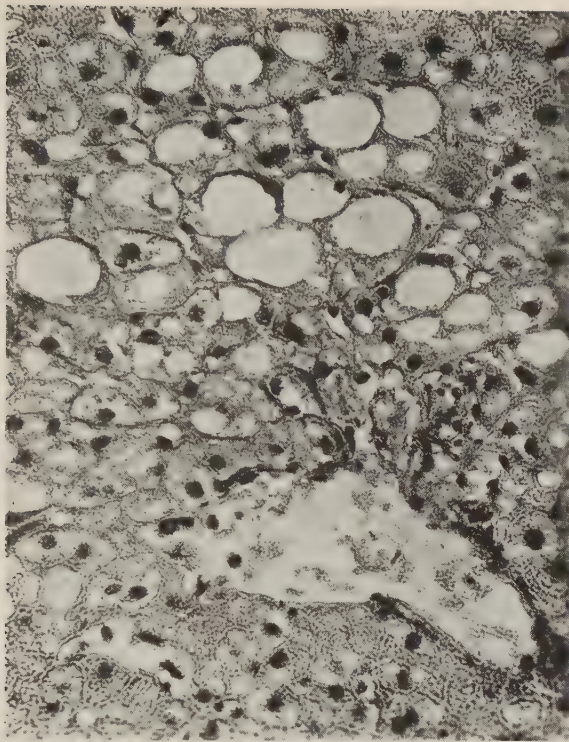


FIG. 7. Case 4. Biopsy specimen of liver. One lobe shows marked, large-globular fatty degeneration of the parenchymal cells. Sparse infiltration of lymphocytes in the periportal connective tissue.

Magnification about $300\times$.

excretion 0.37 g. Bilirubin tolerance: serum bilirubin before test 0.8 mg/100 ml; 3 min. after injection of 0.05 g of bilirubin: 1.3 mg/100 ml; 4 hrs after injection: 0.8 mg/100 ml. Retention: 0.

Thyroid function: protein-bound iodine in serum 7.1 γ %. Tracer test with radioactive iodine (0.05 mC I^{131} by mouth): uptake in thyroid after 24 hrs: 49 %; urinary excretion in first 24 hrs: 28 %.

Electromyographic examination (Docent L. Kirstein). Recordings were made from the left gastrocnemius and the right biceps brachii muscle. On insertion, the tracings showed — in addition to the normal action potentials — scattered peaked potentials with an amplitude of 200–300 μ V and a duration of 10–15 msec. On maximal voluntary contraction, only interference activity by action potentials of normal duration was seen in the tracing from the gastrocnemius muscle. The tracing from the biceps brachii showed, in patches, a dominant incidence of potentials with a duration of 1 1/2–2 msec. and an amplitude of 300–400 μ V. Both the normal action potentials and those of short duration were recorded in the form of interference activity. Thus, the electromyograms of both muscles were pathologic; the appearance of the tracing from the biceps brachii was in agreement with that seen in myopathy.

Electroencephalographic examination (Docent L. Kirstein). Bipolar recording with 21 electrodes. Postcentrally, the dominant activity had a frequency of 9 1/2/sec. and an amplitude from 30 to 50 μ V; this activity was symmetric and was normally blocked by visual stimulation. No pathologic activity. No change was recorded during hyperventilation. Normal tracing.

Histologic examination of biopsy specimen from the liver (Dr. F. Wahlgren): see Fig. 7. The acinar markings were fairly indistinct. In the peripheral parts of the acini, moderate fatty degeneration of the liver cells was seen at some sites. In other respects, these cells exhibited no distinct changes. The intra-acinar capillaries were collapsed and devoid of blood. No swelling of Kupfer's cells. The periportal connective tissue was possibly somewhat more plentiful than usually, and was sparsely infiltrated by mononuclear, lymphocyte-like cells. Nothing abnormal was found in the bile ducts and vessels.

TABLE 17

	D a y						
	1	2	3	4	5	6	7
	0.7	1.0	0.7	-----	0.9	1.2	0.9
Serum bilirubin mg/100 ml							
Urinary urobilin range of dilution	8-16	4-8	16-32	32-64	32-64	512-1064	64-128
Diet	-----	-----					-----

----- ordinary hospital diet

..... low-carbohydrate diet

TABLE 17. Case 4. Serum bilirubin and urinary excretion of urobilin during one week on various diets.

Histologic examination of biopsy specimen from muscle of left calf (Dr. F. Wahlgren). The muscle fibres were of normal thickness and stained normally. At some sites, the sarcolemmal nuclei seemed to be more plentiful than usually, and the collagen fibres were somewhat increased. There was possibly a disappearance of a few muscle fibres at these sites. An accumulation of muscle nuclei seen in one place indicated that this was actually the case. The walls of the arterioles were distinctly thickened and their lumen constricted. Thus, their appearance was that found in arterial hypertension. No other cell changes were observed, nor was there any inflammatory accumulation of cells.

Determination of the *myoglobin content* of a biopsy specimen of the gastrocnemius muscle (Ing. Å. Åkesson): 1.60 %.

Provocation experiment by low-carbohydrate diet. After the patient had been in hospital for a week and had shown no indications of myoglobinuria, he was placed on a low-carbohydrate diet. Administration of this diet for four days produced no muscular symptoms in the form of pain or tenderness, nor any limitation of movement. For the serum bilirubin and urinary urobilin values, see Table 17.

Roentgenologic examinations. Lungs: nothing abnormal. Oesophagus: no varices. Abdomen: no definite enlargement of the spleen.

The *electrocardiogram* was normal.

Case 5. A man, b. July 10, 1901. Manual worker.

Heredity. No history of any similar disease in the family.

Previous history. The patient's health had mainly been good and he had been able to do heavy manual work without difficulty. According to his relations, he was addicted to alcohol. In the middle of May 1951, there was sudden "swelling" of the right lower leg, which subsided after 5 or 6 days. Similar "swelling" of the left lower leg developed in the middle of July. It was accompanied by splitting pain on extension of the leg and a feeling of stiffness in the right leg.

He was admitted to the medical department of Östersund Hospital on July 20. On admission, his discomforts had lessened. Examination showed slight reddening of the left lower leg and foot, with moderate oedema of the subcutaneous tissues, most conspicuous distally. There was slight tenderness of the calf muscles of both legs. Since thrombosis was suspected, phlebograms were taken of both lower legs; they showed normal conditions. Oscillograms from both lower legs disclosed nothing abnormal. The condition was therefore diagnosed as oedema of the left leg of unknown origin. The patient was discharged on August 4, free from symptoms and signs.

In October 1953, swelling and tenderness once again appeared in both calves, but subsided after a day or so.

Last illness. On March 3, 1954 there was a feeling of stiffness in both calves, which gradually swelled and became hard, so that the patient was finally unable to move his feet. On March 7, he had extremely severe pain in the lower legs and complained of cramp in the back of his knees. His temperature was 37.9° C. The physician called in suspected bilateral thrombosis, and therefore had the patient admitted to the medical department of Östersund Hospital.

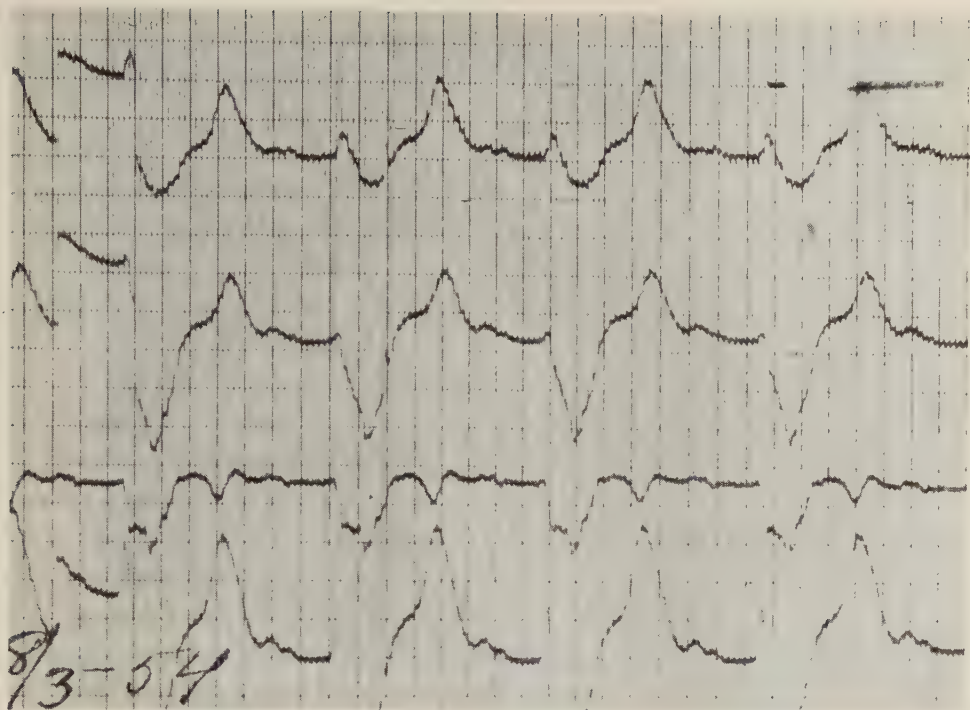


FIG. 8. Case 5. ECG recorded 3 hours before death. Bundle-branch block. QRS complex 0.20 sec. High, peaked T waves. Serum potassium: 12.3 mEq/L.

Physical examination on admission on March 7 showed no systemic disturbances. *Heart*: sounds pure, rhythm normal; pulse rate 78/min. *Blood pressure*: 150/90 mm Hg. *Lungs*: nothing abnormal. *Abdomen*: nothing abnormal. *Legs*: there was considerable swelling of the entire calf muscles of both legs; they were firm in consistency and were tender all over. The pulsations of the dorsalis pedis were normal bilaterally. The circumference of both calves was 39 cm. There was considerable limitation of both volar and dorsal flexion.

Dark-brown urine was passed; the benzidine test was strongly positive, and spectroscopic examination (Prof. G. Blix) showed the presence of myoglobin.

On the following morning (March 8) the patient's general condition was affected. There was cold sweat, and he complained of aches in both calves. The heart rhythm was regular and the pulse rate 78/min. (ECG: see Fig. 8). Blood pressure: 130/90 mm Hg. For blood laboratory data, see Table 18. Around noon, he suddenly became acutely ill, with laboured breathing and a weak pulse. Death took place within a few minutes.

Extract from autopsy report (Östersund Hospital). The calf muscles had a "fish flesh" appearance. The thigh muscles and the biceps brachii showed similar changes, although they were less marked.

Autopsy specimens were also sent for examination to Dr. F. Wahlgren, Södersjukhuset, Stockholm, who made the following report.

Heart muscle. The muscle fibres were somewhat hypertrophied. Small, dense scars were visible in several places in the interior of the ventricular septum. There were no signs of endocarditis. Sections from the anterior wall of the left ventricle and the anterior parts of the septum showed a number of small connective tissue scars of varying age. They were presumably small healed infarctions. The anterior descending limb of the left coronary artery was greatly sclerosed, causing constriction of its lumen.

On macroscopic examination, the *calf muscles* had a greyish-white colour. The muscle fibres were swollen and lacked striation. They had a tendency to fragmentation. Between the fibres was a marked infiltration of fluid with a protein content, containing numerous inflammatory cells, chiefly neutrophil

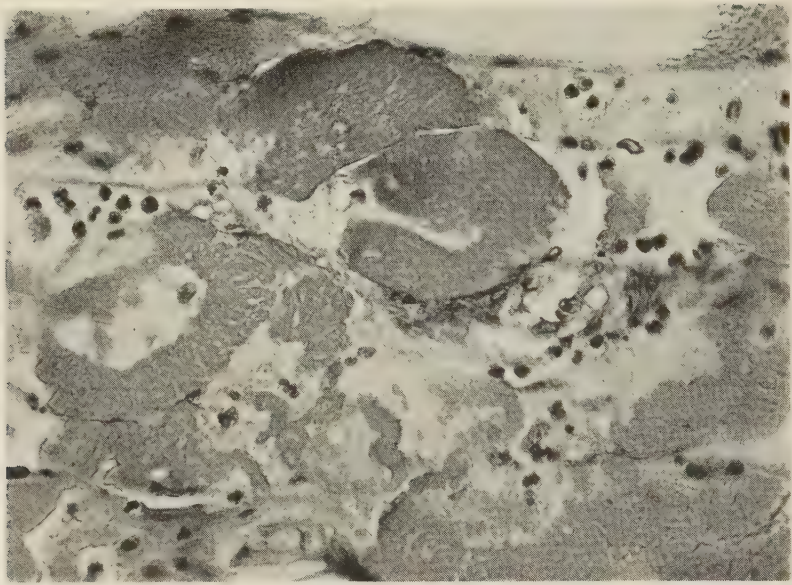


FIG. 9. Case 5. Autopsy specimen of calf muscle, showing markedly necrobiotic muscle fibres. Oedema and infiltration of leukocytes between the fibres. Magnification about 300 $\times$.

leukocytes. No micro-organisms were found on gram-staining. No vascular changes were visible in the muscles (Fig. 9). Microscopically, the specimen of *thigh muscle* was reddish-brown. The majority of muscle fibres exhibited normal striation. At scattered sites, individual fibres seemed, however, to be swollen and were sometimes broken up into hyalin masses with no visible striation. In the vicinity of these fibres, the sarcolemmal cells appeared somewhat swollen. In one place, a small cluster of leukocytes was present close to a vessel. No other inflammatory accumulation of cells was seen, nor were there any vascular lesions. The *biceps brachii* had essentially the same appearance, although no inflammatory accumulation of cells was present.

TABLE 18

	7/3-54	8/3-54
Hgl %		98
R. B. C.		5,600,000
W. B. C.	9,900	15,800
S. R.		17 mm/1 hr
CO ₂ vol. %		25
Serum potass. mEq./L		12.3
Serum sodium mEq./L		136
N. P. N. mg/100 ml		57
Serum protein %		8.2
Blood sugar mg/100 ml		90
Haematocrit		52

TABLE 18. Case 5. Blood determinations.

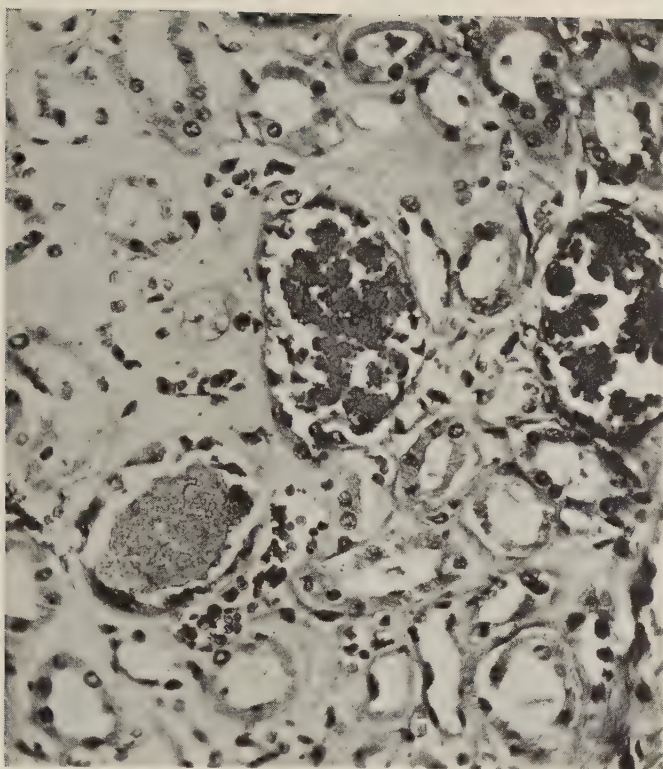


FIG. 10. Case 5. Autopsy specimen of kidney. Three of the second convoluted tubules contain myoglobin casts. Degenerative lesions of the tubular epithelium. Magnification about 300 $\times$.

Liver. The acinar markings were distinct. At some sites, the liver cells showed fatty degeneration in the form of large globules. The intra-acinous capillaries were fairly wide and devoid of blood. There was no swelling of Kupffer's cells. No increase in the periportal connective tissue. Nothing pathologic was found in the bile ducts or vessels. No iron pigment was present. Histologic diagnosis: slight fatty degeneration.

No noteworthy changes were visible in the *spleen*. No iron pigment was demonstrable.

Kidneys (Fig. 10). The glomeruli appeared to be normal. The epithelial cells of the convoluted tubules had a finely-granulated appearance. At some places in the second convoluted tubules there was "tröpfiges Hyalin", *i.e.*, fine granules which stain positively with fibrin stain. In some of these tubules, as well as in the collecting tubules, casts with a fairly compact appearance and yellowish-brown colour were present. The vessels in the medulla and in the borderline zone between the cortex and the medulla were somewhat engorged. There were no changes in the vessel walls. Thus, there were degenerative lesions of the tubular epithelium, as well as fairly numerous casts, presumably consisting of myoglobin.

Case 6. A boy, b. Feb. 9, 1942.

Heredity. The patient is no. 1 of 3 siblings. His parents and siblings are healthy. There are no known cases of muscular disease in the family.

Previous history. During his first two years of life, development was normal. After he was 2 years old, he began to manifest some motor disturbances. His movements became clumsy and he started to walk on tip-toe. He also had difficulty in getting up into an erect position after bending forwards. These disturbances were particularly noticeable when he was 4 to 5 years old. The muscular weakness prevented him from joining in games with other children, from skiing and so on. During the past few years, the muscular weakness has been less conspicuous, although he is considerably weaker than his brother who is one year younger.

Myoglobinuria. On Jan. 31, 1954 the patient was out in the woods with his father and had to make great efforts to keep up with him. He became tired, and his calf muscles ached and were tender. In the evening, he passed dark-brown urine. He had some nausea, but there was no vomiting or fever.

He was admitted to the Paediatric Clinic of Jönköping Hospital on February 1. On admission, his urine was paler but was still discoloured. Physical examination showed no systemic disturbances. *Heart*: sounds pure, rhythm regular. *Lungs*: nothing abnormal. *Abdomen*: nothing abnormal. *Reflexes*: pupillary, patellar and Achilles reflexes normal. Babinski's sign negative bilaterally. There was generalized muscular weakness, as well as distinct pseudohypertrophy of the *calf muscles*; their consistency was hard and firm. No definite paresis was found.

Blood tests: haemoglobin 104 %. R. B. C. 5,200,000. W. B. C. 5,100. S. R. 3 mm/1 hr. Non-protein nitrogen 35 mg/100 ml.

Urinalyses: tests for protein and reducing substance negative. Nothing pathologic in the sediment. Bile pigments: the Schlesinger, Ehrlich, Bouma and Hay tests gave negative reactions. Spectroscopic examination (Prof. G. Blix) showed the presence of myoglobin.

A diagnosis of muscular dystrophy was made. The patient was discharged from hospital on February 6. Since then, there has been no recurrence of the symptoms of myoglobinuria, but he has not indulged in any hard exercise.

At a check-up examination in February 1955, there was still generalized muscular weakness and distinct pseudohypertrophy of the calf muscles. Two determinations of the spontaneous 24-hour urinary excretion of *creatinine* and *creatinine* were made at this time. On the first occasion he excreted 105 mg of creatine and 750 mg of creatinine, and on the second 58.5 mg of creatine and 605 mg of creatinine.

The urinary excretion of *17-ketosteroids* was 3.5 mg/24 hours and that of *corticosteroids* 5.6 mg/24 hours. The chromatogram was normal.

Histologic examination of a biopsy specimen of the right calf muscle (Dr. F. Wahlgren). The muscle fibres lay far apart; they were separated both by oedema of the mesenchymal tissue and by adipose tissue. Most of the fibres were of about the usual width, but occasional thicker fibres were visible. In general, the striation was distinct. Occasional fibres had a homogeneous appearance; there were probably slight degenerative lesions. No waxy degeneration was, however, demonstrable. The mesenchymal cells between the muscle fibres were swollen; at some sites, scattered leukocytes were present. In a small band-shaped area, there were a few, fairly large, elongated and irregularly shaped cells with abundant, basophil cytoplasm. The cell nuclei were large and oval and contained plentiful chromatin; they lay peripherally in the cell body. These cells were presumably remains of necrosed muscle cells. No vascular changes were visible.

The muscle thus showed signs of slight degenerative lesions, in the form of oedema and a sparse infiltration of inflammatory cells in the stroma. Pseudohypertrophy was manifested by the infiltration of fat between the muscle fibres.

Determination of the *myoglobin content* of a biopsy specimen from the calf muscle (Ing. Å. Åkesson) showed it to be 0.57 %.

3. Discussion

In Case 4, the history differs essentially from that in the familial form of myoglobinuria. Thus, the patient had never noticed that exertion had brought on an attack, nor that an attack was more liable to occur when he exerted himself on an empty stomach, whereas these were salient features of the familial form. On the other hand, the individual attacks exhibited great similarities to those in Cases 1—3. They were associated with severe pain and tenderness in the muscles, and a rise in temperature to 39 or 40° C. The patient was incapacitated for a considerably longer time than were Cases 1—3. After two of the attacks, he was unable to work for three months, and after another for over four months. In between the attacks, he was fit and was able to do heavy manual work.

His condition had been diagnosed as acute nephritis and as lumbago, and on one occasion poliomyelitis was suspected. A curious feature is that each of the attacks occurred at Christmas, six years in succession.

After four days on a low-carbohydrate diet, no muscular symptoms appeared, nor was there any urinary excretion of creatine. On the other hand, the urinary content of urobilin was pathologic, and there was a slight rise in the serum bilirubin, presumably to be ascribed to liver damage.

The urinary findings were the same as in Cases 1—3. During the attacks, there was proteinuria, the highest value being 0.2 per cent, and the sediment contained a maximum of 5—8 red blood cells per visual field. The discoloration of the urine often lasted for a week.

During the first attack of myoglobinuria in 1945, the renal damage was considerably more severe than in any of the familial cases. The non-protein nitrogen was then up to 180 mg/100 ml, but the renal injuries healed completely. During the attack in 1949, the highest value recorded for the non-protein nitrogen was 44 mg/100 ml. Concentration and dilution tests showed concentration to 1,013 and dilution to 1,009, *i.e.*, bordering on isosthenuria. The creatinine clearance test showed good filtration (132 ml/min.). Proteinuria was present only during the first few days in hospital. Thus, one week after the beginning of the attack, the urinary findings were the same as in Case 3: a normal urinary output, no proteinuria, nothing pathologic in the sediment, a practically normal non-protein nitrogen level and normal creatinine clearance but, notwithstanding, isosthenuria.

Consequently, it is probable that the renal damage associated with myoglobinuria may be overlooked if the patient is not admitted to hospital until a few days after the onset of the attack. By that time, if the urine is no longer discoloured, the reaction to tests for protein will be negative, since this reaction is positive only when there is myoglobinuria. In the patient in question, no signs of renal damage were disclosed by the concentration and dilution test made during an asymptomatic interval in 1954, the concentration then being 1,027 and the dilution 1,004.

Blood tests made at the same time showed normal values for the haemoglobin level, R. B. C., W. B. C., reticulocyte and thrombocyte counts and the differential leukocyte count. A white blood cell count was made during the attack in 1949, and was then normal (5,400). A slight rise in the S. R. (to about 20 mm/1 hr) was sometimes found in between the attacks; this was probably due to the liver damage. During the two attacks in which the S. R. was determined, it was 55 and 95 mm/1 hr, respectively. No disturbances in the electrolyte balance were found in between the attacks.

Nothing abnormal was found in the circulatory organs. During an asymptomatic interval, there were no electrocardiographic changes. The blood pressure was normal and was not affected by the attacks.

Glucose tolerance tests showed a normal curve both in 1950 and in 1954. In the adrenalin tolerance test, there was only a slight rise in the blood sugar level, probably due to liver damage with a decrease in the liver glycogen. Studies of the creatine and creatinine metabolism disclosed nothing pathologic. The patient excreted no creatine in the urine, neither spontaneously, after oral administration of creatine, nor on a

low-carbohydrate diet. Thus, in this patient, the glucose tolerance and the creatine metabolism differed essentially from the conditions in the familial cases.

Studies of the liver function revealed definite indications of liver damage. The thymol turbidity was 10.5 units, the Takata reaction was positive, there was a pathologically high peak in the γ globulin fraction in the electrophoresis curve, and histologic examination of a biopsy specimen also showed liver damage. In the bilirubin tolerance test, no retention took place, despite the evident impairment of liver function. This contrasted to the findings in Cases 1—3, all of whom had a high retention value, despite indications of slight liver damage only.

In Case 4, no mental changes were observed during the attacks or during the asymptomatic intervals. Neurologic examinations showed no abnormalities, and no signs of muscular dystrophy were present. At electromyographic examination during an asymptomatic interval in 1954, a definitely pathologic curve of the myopathy type was recorded. It was presumably due to residual damage following the muscle injuries during the attacks of myoglobinuria. Examination of a biopsy specimen of muscle in 1954 showed distinct histologic changes, although it had been four years since the last attack. In Cases 1—3, electromyographic recordings and examination of biopsy specimens disclosed nothing pathologic, either during the attacks or in between them. Consequently, both the liver and the muscle damage seem to be more severe in Case 4 than in the patients with the familial form of myoglobinuria.

In Case 4, no toxic factors which might have precipitated the attacks were found in the history. Moreover, toxic injuries as a cause of myoglobinuria are unknown in man. For example, although muscle injuries in addition to liver damage occur in phosphorus poisoning (Adams *et al.* 1953), myoglobinuria has never been verified.

To sum up the results of the investigation in Case 4, the following statement may be made. The patient has paroxysmal myoglobinuria, differing from the familial form of the disease in three respects. (1) The attacks have no relation either to muscular exertion or to a low-carbohydrate diet. (2) The glucose tolerance is normal. (3) The creatine metabolism is normal.

No disturbance in carbohydrate metabolism was found. It is therefore probable that the pathogenesis is not the same in Case 4 as in the familial form of the disease.

Case 5 presents several interesting features. Four days before the appearance of myoglobinuria, severe pain developed in the muscles of both calves, which were greatly swollen and oedematous. Similar manifestations had appeared on three earlier occasions, although no myoglobinuria was found. It may be recalled that, both in Haff disease and in lumbar paralysis in the horse, there may be typical attacks with muscular symptoms, although no myoglobinuria is present. It therefore seems highly probable that the patient's earlier symptoms were, in fact, manifestations of the disease, although myoglobinuria did not appear until the last, fatal attack.

On this occasion, the symptoms were initially mild and there were no constitutional disturbances. It was not until the sixth day after the onset that a sudden exacerbation

took place. Within about an hour, the patient broke out into a cold sweat, his respiration became laboured and his pulse feeble, and he died.

At autopsy, the calf muscles presented marked pathologic changes. They had the greyish-white colour — the “fish flesh” appearance — often described in myoglobinuria. Microscopic examination showed swelling of some of the muscle fibres; they were swollen, lacked the normal striation and had a tendency to fragmentation. Between the fibres was an infiltration of fluid containing numerous leukocytes. Obviously, this might have been an inflammatory reaction. The same phenomenon is, however, found in paralytic myoglobinuria in animals, the quantity of leukocytes being proportional to the duration of the disease. It is regarded as a phagocytic phenomenon. The thigh muscle exhibited similar lesions, although it had the normal colour; this also applied to the biceps brachii, except that no inflammatory cells were present.

Changes characteristic of tubular nephrosis were found in the kidneys, and there was slight fatty degeneration of the liver.

The high serum potassium level in this case is particularly noteworthy. The appearance of the electrocardiogram (Fig. 8) was compatible with the assumption that hyperpotassaemia was present.

Such hyperpotassaemia is explainable on the grounds of the rapid disintegration of muscle. The muscles have a high potassium content (450 mg/100 g); rapid disintegration therefore implies a considerable diffusion of this substance into the blood stream. It is probable that, in this case, the renal damage found at autopsy contributed to the high serum potassium level. As far as I have been able to ascertain from the literature, death has not been caused by verified hyperpotassaemia in any earlier case of non-traumatic myoglobinuria (*cf.* p. 70).

As may be inferred from the history, Case 6 was a 13-year-old boy who, soon after he was two years old, began to exhibit some motor disturbances. He started to walk on tip-toe and also had difficulty in rising after bending forwards. These disturbances were most marked between the age of four and five.

At examination in February 1955, he still exhibited general muscular weakness and definite pseudohypertrophy of the calf muscles. Among the findings at histologic examination of a biopsy specimen of calf muscle were indications of pseudohypertrophy, caused by infiltration of adipose tissue between the muscle fibres. The myoglobin content of the calf muscle was also strikingly low, *i.e.*, 0.57 per cent as compared to the normal 2.73 per cent.

All these manifestations must presumably be ascribed to the muscular dystrophy.

The patient's attack of myoglobinuria occurred after muscular exertion; this is in agreement with the conditions in cases of myoglobinuria combined with muscular dystrophy reported in the literature.

The urinary excretion of 17-ketosteroids was normal, in contrast to Acheson & McAlpine's case of muscular dystrophy combined with myoglobinuria, in which the output of 17-ketosteroids was pathologically raised.

4. *Summary*

An account is given of three cases of myoglobinuria, and the findings are discussed. Two of the cases are of the unclassifiable type; one of these patients died during an attack of myoglobinuria, presumably of hyperpotassaemia. In the third case, there was coincident muscular dystrophy.

In Part One, Chapter I, a short survey is given of the chemical and physiological properties of myoglobin. Its absorption spectra are only slightly dissimilar to those of haemoglobin. The greatest difference is found in the carboxy compounds, the band being $579\text{ m}\mu$ for carboxymyoglobin and $568\text{ m}\mu$ for carboxyhaemoglobin. The molecular weight of myoglobin is 17,200 and that of haemoglobin 68,000; this explains why its excretion through the kidneys is 25 times more rapid than that of haemoglobin. The myoglobin content of the muscles is only inappreciably influenced by various pathologic conditions, the concentration being determined mainly by the physical activity of the muscles.

Chapter II comprises a brief account of various conditions in which myoglobinuria is found in domestic animals. Particular interest is focused on paralytic myoglobinuria in the horse.

In Chapter III, a report is given of earlier classifications of the myoglobinurias, and a new classification is suggested. Apart from Haff disease and the various traumatic forms of myoglobinuria, descriptions are found in the literature of 20 cases of myoglobinuria (15 males and 5 females), 12 of them verified spectroscopically. A short account is given of these 20 cases. In 6 of them, myoglobinuria is associated with muscular dystrophy; in these cases muscular weakness often develops during the attack of myoglobinuria, but is confined to the muscles affected by the dystrophic process.

Part Two consists of a description and discussion of the writer's 6 cases of myoglobinuria. The case material and the methods used in the investigation are presented in Chapter IV.

Three of the patients suffer from an earlier unreported familial form of paroxysmal myoglobinuria without muscular dystrophy (Chapters V and VI). The disease is combined with a disturbance in carbohydrate metabolism, indicated by the following:

1. The patients' statements that hard exercise on an empty stomach invariably precipitates an attack.
2. Experimental provocation of attacks by a low-carbohydrate diet.
3. Pathologic glucose tolerance curves.
4. Pathologic creatine metabolism.

The disturbance in creatine metabolism differs from that found in muscular dystrophy, in that the patients have a high urinary output not only of creatine, but also

of creatinine. During the attacks of myoglobinuria, there is often a transient rise in temperature to 39 or 40° C, leukocytosis and a rise in the sedimentation rate, as well as tachycardia and a slight rise in blood pressure of fairly short duration. Mental symptoms are sometimes present. There is also intense thirst. An inability to produce diluted urine, with no impairment of concentration, develops several years after the onset of the disease. Examination of biopsy specimens shows no histologic changes in the muscle. An exacerbation of the myoglobinuria occurs in association with thyrotoxicosis.

The three other cases of myoglobinuria (Chapter VII) differ considerably from the familial form. In one of these cases, the investigation has been made with particular consideration to a comparison with the familial form. The patient in question is found to have a normal glucose tolerance curve and normal creatine metabolism. An attack cannot be provoked by means of a low-carbohydrate diet, and nothing is found in the history to suggest that myoglobinuria is more apt to appear after exertion on an empty stomach. It is therefore concluded that the pathogenesis differs from that in the familial form.

One patient died during an attack of myoglobinuria. The direct cause of death is considered to be hyperpotassaemia, due to a release of potassium from the muscles into the blood stream.

The third patient is found to exhibit definite signs of muscular dystrophy, in the form of generalized muscular weakness and pseudohypertrophy of the calf muscles.

In these three cases, examination of biopsy specimens shows distinct histologic lesions of the muscles.

The following points are also stressed with respect to the writer's six cases of myoglobinuria:

1. The attacks often cause renal damage; in the severe ones there is a rise in the non-protein nitrogen, the milder ones being associated with isosthenuria only.
2. During an attack, there is a risk of hyperpotassaemia, which may be life-threatening, particularly if there is coincident renal impairment.
3. Some degree of liver damage is present in all five cases in which studies of the liver were made.
4. The attacks are apt to be misinterpreted as glomerulonephritis.

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